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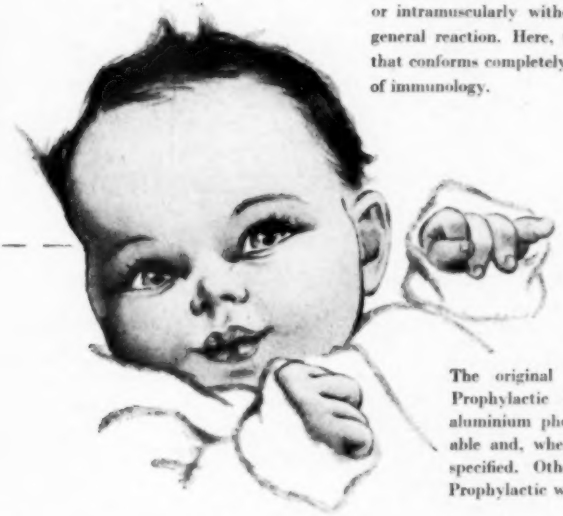

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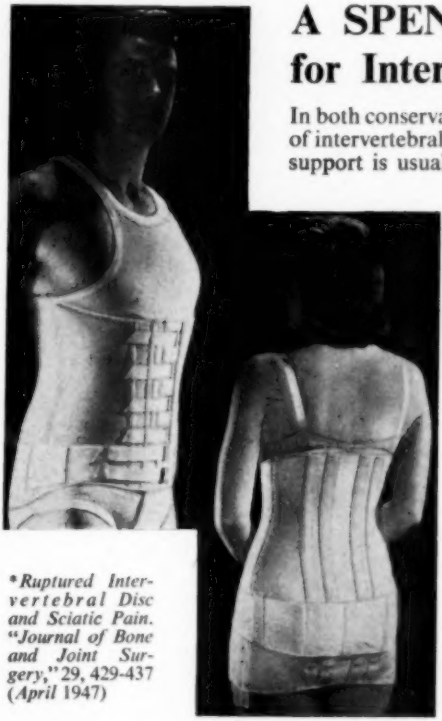

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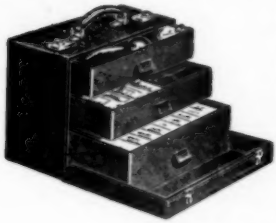

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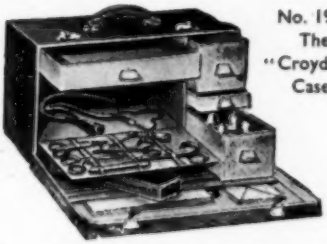

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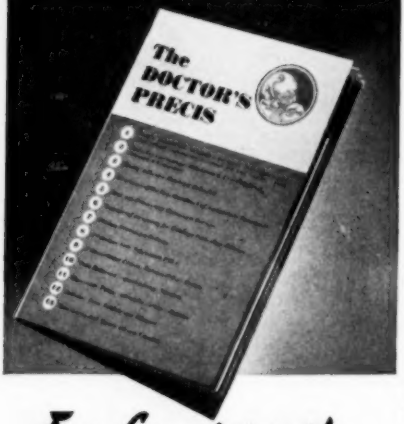

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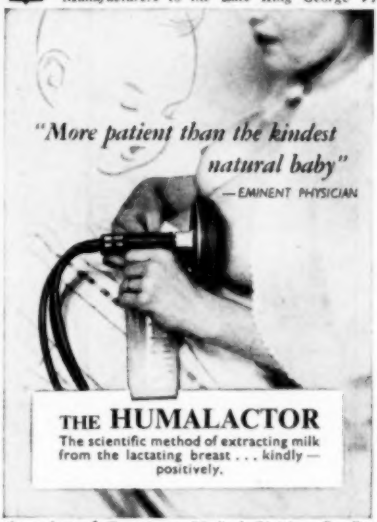
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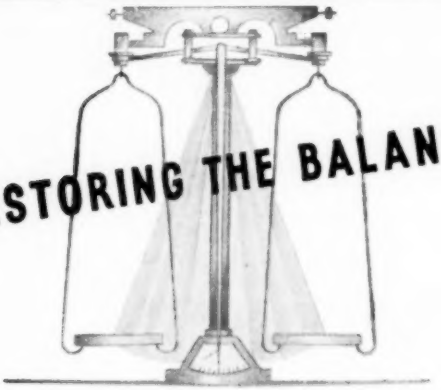

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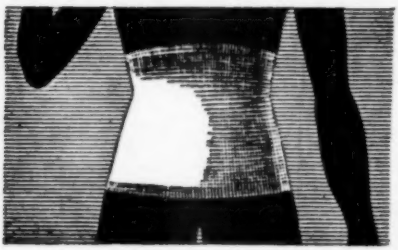

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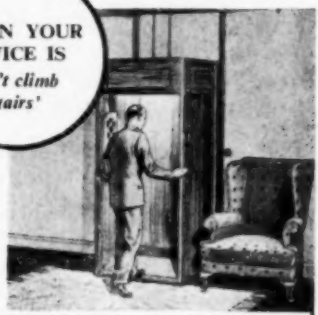

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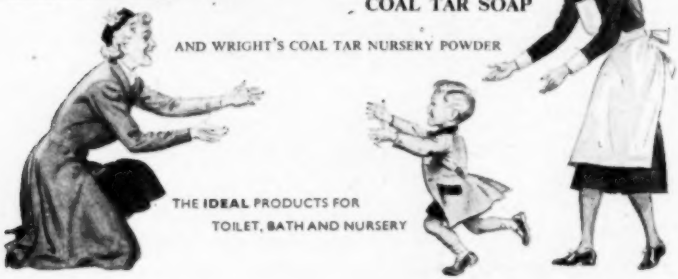

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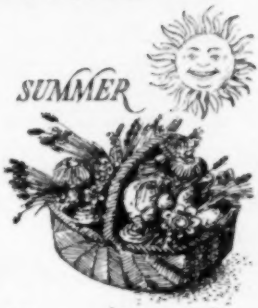

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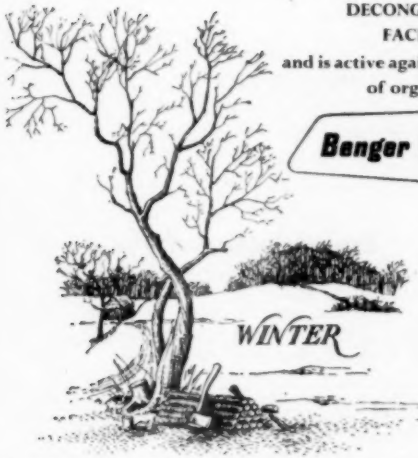

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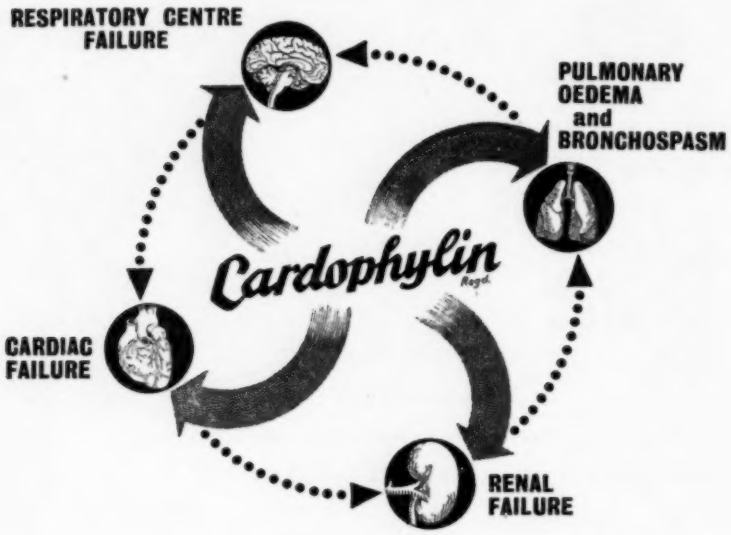

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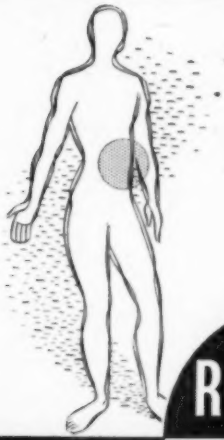

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'LIVEROID'

A concentrated preparation of the uncoagulated juice of liver, fortified with iron and glycerophosphates.

Bottles—3¾ and 8 fl. oz.

'LIVOX'

Capsules containing liver concentrate reinforced with B group vitamins and minerals.

Bottles of 100 and 500

'ERYTHOID'

Desiccated gastric tissue —

Bottles 5 oz. and 8 oz.

LITERATURE GLADLY FORWARDED UPON REQUEST

OXO LIMITED (Medical Dept.)
Thames House, Queen Street Place,
London, E.C.4. Phone: Central 9781

When prescribing

PENICILLIN *and other* STERILE PREPARATIONS

Don't forget to state "C.G. Brand."

Our laboratories operate under Ministry of Health licence (TSA) No. 174. Modern methods and equipment are used and there is constant direct supervision by expert qualified staff. Potency and sterility are absolutely assured. The following are included in our range :—

PENICILLIN ORAL TABLETS— all potencies from 10,000 units to 1,000,000 units per tablet

PENICILLIN AURAL BOUGIES— containing 10,000 units

PENICILLIN GAUZE—in tins of ten pieces

OCULENTA
OINTMENTS
INJECTIONS
EYE DROPS, etc., etc.

Also Pyrogen-free distilled water for the preparation of injections

A PRODUCT OF
Curson Gerrard & Co. Ltd.
OLDBURY BIRMINGHAM

Nervous sedation is required in conditions such as . . .

Whooping-cough
Bronchial asthma
Juvenile hypertension
Eczema and pruritus
Post-concussional disturbances

CALCIBRONAT

(Calcium bromido-lactobionate)

provides sedation, brings about undisturbed sleep and restores nervous equilibrium. Calcibronat allows a combined and synergistic calcium and bromide therapy devoid of any side-effect.

SWEETENED GRANULES ★ EFFERVESCENT TABLETS
AMPOULES

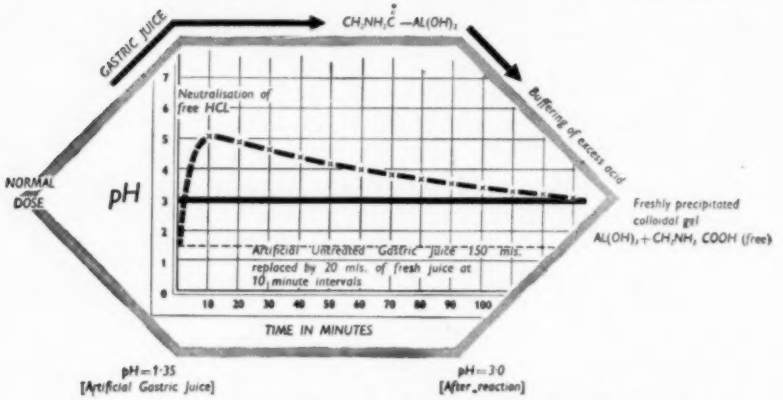
Literature and samples on request

SANDOZ

SANDOZ PRODUCTS LIMITED

134, *Wigmore Street* *London, W.1*

Gastro-Duodenal Ulceration



Amino Acid and Antacid Therapy

TABNET

BRAND

DIHYDROXY ALUMINIUM AMINOACETATE

The Medical Management of Gastro-Duodenal Ulceration

presents a positive approach to the medical management of gastro-duodenal ulceration in providing dihydroxy aluminium aminoace ate.

The reaction of this new buffering agent under conditions of gastric hyperacidity is threefold:—

It rapidly neutralises excess acid bringing quick relief from pain.

A freshly precipitated colloidal gel is formed which protects the exposed gastric submucosa from the action of the digestive ferments.

By slow hydrolysis the amino acid, glycine, is released, which in addition to the free glycine in the formula assists in the promotion of healing.

FORMULA: Dihydroxy aluminium aminoacetate 250 mgms.
Glycine . . . . . 30 mgms.

Prescribe TABNET by name

TABNET
BRAND
DIHYDROXY ALUMINIUM AMINOACETATE

Available in bottles of 100 and 1,000 tablets

Literature available on request from the Medical Department:

CALMIC LIMITED · MANUFACTURING CHEMISTS · CREWE · Tel: CREWE 3251-5

Ortho proudly presents . . .

Preceptin®

VAGINAL GEL

the simple method of contraception that needs no diaphragm . . .

Physicians and patients have long been demanding a simpler contraceptive method than jelly and diaphragm.

the barrier is in the base

To replace the function of the diaphragm, a new and better physical barrier, incorporated into the Gel itself, was needed—one that could be depended on to cover the cervical os effectively. The new base of PRECEPTIN, achieved by blending recently developed synthetic gel-forming agents, meets this requirement, making it possible to do away with the diaphragm.

clinically proved

Of 3760 patients using Preceptin Gel - 99.2 per cent received complete protection

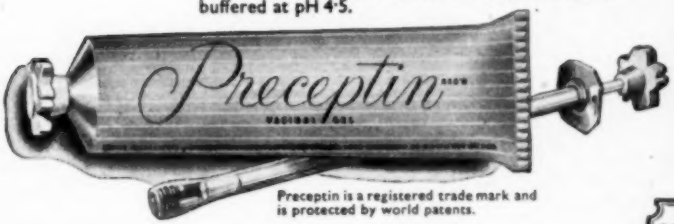
Preceptin's new base :

1. **adheres well to the moist cervical mucosa — forms a persistent, adherent physico-chemical barrier over the cervical os.**
2. **is more miscible with semen—means greater spermicidal potency.**
3. **rapidly releases active spermicides—enables Preceptin to kill sperm on contact.**

Preceptin Vaginal Gel

Used with measured-dose applicator.

COMPOSITION : PRECEPTIN contains the active spermicidal agents p-diisobutylphenoxypolyethoxyethanol 1·00% and ricinoleic acid 1·17% in a synthetic base buffered at pH 4·5.



Preceptin is a registered trade mark and is protected by world patents.

Ortho Pharmaceutical Limited

HIGH WYCOMBE · BUCKINGHAMSHIRE · ENGLAND

Available through the Medical Profession only

BEREX

Reg. Trade Mark

SUCCINATE-SALICYLATE THERAPY

Licensed under DOLCIN Patent. Patented in Great Britain 642971

IN TABLET FORM

For the relief of symptoms and aid in the control of the systemic metabolic disturbances found to be associated with Arthritis and all Rheumatic disorders

INDICATIONS

1. Rheumatic Fever.
2. Articular Rheumatism (including Rheumatoid and Osteo-Arthritis).
3. Non-articular Rheumatism (including Fibrositis, Neuritis and Sciatica).
4. Arthritis associated with the menopause.
5. Gout.

FUNCTION

A stimulating effect on cellular respiration and respiratory enzyme systems, together with an increase of oxygen utilisation by the tissues (impairment in tissue oxygenation having been demonstrated in arthritis).

Since Berex is non-toxic it may be prescribed whenever massive salicylate therapy is indicated.

BEREX combines the following advantages: Prompt relief of symptoms; correction of impaired tissue oxidation; obviation of salicylate toxicity; suitability for protracted administration.

Professional sample and literature on request to:

BEREX PHARMACEUTICAL CO.
MEDICAL DEPARTMENT, 109 JERMYN STREET, LONDON, S.W.1

'MYSOLINE'

Trade Mark

THE NEW ANTICONVULSANT

For Grand Mal Epilepsy

'Mysoline' can effectively control the convulsive seizures of grand mal epilepsy.

In a trial of 40 patients who were continuing to have major epilepsy despite other forms of treatment, 80% were improved by 'Mysoline' and 30% were completely freed from attacks of all kinds.

This result was achieved with the minimum of side-effects and there was an improvement in the mental alertness, outlook and general well-being of the patients.*

* See *Lancet*, (1952), i, 742

The potentialities of 'Mysoline' in petit mal and psychomotor types are still under investigation.

'Mysoline' (5-ethyl-5-phenyl-hexahydropyrimidine-4:6-dione) is issued in tablets of 0.25 *gramme. Containers of* 100 *and* 1,000.

Further information may be obtained through your nearest I.C.I. Sales Office—London, Bristol, Birmingham, Manchester, Glasgow, Edinburgh, Belfast and Dublin.

IMPERIAL CHEMICAL (PHARMACEUTICALS) LTD.

A subsidiary company of Imperial Chemical Industries Ltd.

Wilmslow **Manchester**

Ph.297

For Nasal Congestion

'Neophryn' (active principle a sympathomimetic substance) is an ideal local application for nasal congestion—particularly in children. It causes no impairment of ciliary function, no local irritation and no secondary congestion. Three or four drops are instilled into each nostril. (The patient should lie flat with chin raised and neck fully extended, and maintain this position for two minutes.)

Medical Literature available on request.

NEOPHRYN

BRAND OF NASAL SOLUTION *Trade Mark*

Neophryn is known overseas as Neosynephrine

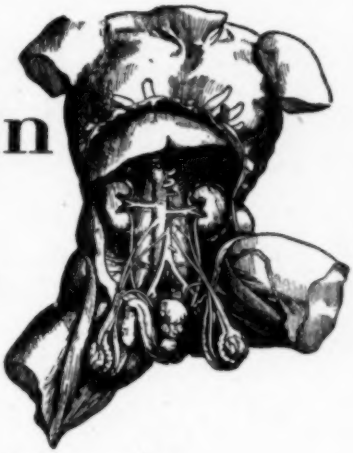
BAYER **PRODUCTS LTD** · AFRICA HOUSE, KINGSWAY, LONDON, W.C.2

Associated Export Company: WINTHROP PRODUCTS LTD., LONDON

Terramycin

in

Urinary Tract Infections



The value of Terramycin in the general field of infective medicine is due to its very wide antibacterial range, its versatility and ease of administration, the rapidity of its action, and its remarkably low toxicity.

In urinary tract infections, the particular value of Terramycin lies both in its ability to reach relatively high concentrations in the urine on low dosage and in a corresponding increase in urine concentration which results from an increase in dose.[1] [2]

INDICATIONS IN URINARY TRACT INFECTIONS

1. Infections due to mixed bacterial flora.
2. Infections resistant to other chemotherapeutic and antibiotic agents.
3. Infections due to Pseudomonas pyocyanea.
4. Infection with anatomical abnormalities or other complicating mechanical factors of the urinary system.
5. For pre-operative and post-operative control of infection in genito-urinary surgery.
6. Infections due to other Terramycin-sensitive organisms.

Terramycin can now be used for all suitable conditions in Hospitals in Great Britain, and the forms at present available include Sugar-Coated Tablets, Elixir, Oral Drops and Intravenous.

REFERENCES:
[1] B.M.J. (Nov. 25), 1950.
[2] Ann. New York Academy Sc. (Sept. 15), 1950.

Pfizer

Full literature is available and will be supplied on request

PFIZER LTD. 47-48, PICCADILLY, LONDON, W.1

Hormone Preparations

for use in Gynæcology and Andrology

OESTROGENS

Tablets of Ethinylœstradiol, B.P.-Boots
0.02 mg., 0.05 mg. or 1 mg.

Tablets of Stilbœstrol, B.P.-Boots
0.1 mg., 0.25 mg., 0.5 mg., 1 mg. or 5 mg.

Injection of Stilbœstrol-Boots
1 ml. ampoules, 1 mg. or 5 mg.

Stilbœstrol Ointment-Boots
0.5 or 1 per cent. in a water-miscible base.

Tablets of Dienœstrol, B.P.-Boots
0.1 mg., 0.3 mg., 1 mg. or 5 mg.

ANDROGENS

Injection of Testosterone Propionate, B.P.-Boots
1 ml. ampoules, 5 mg., 10 mg. or 25 mg.
Also supplied in graduated doses for the desensitization treatment of keratitis rosacea

Tablets of Methyltestosterone, B.P.-Boots
5 mg. or 10 mg.

PROGESTOGENS

Luteostab Brand Injection of Progesterone, B.P.
1 ml. ampoules, 2 mg., 5 mg. or 10 mg.

Tablets of Ethisterone, B.P.-Boots
5 mg. or 10 mg.

Literature and further information obtainable from the Medical Department
BOOTS PURE DRUG CO. LTD., NOTTINGHAM, ENGLAND

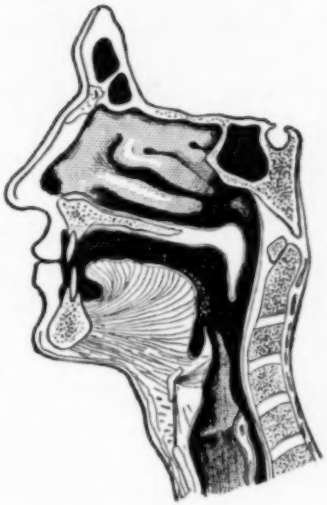
140

THE TREATMENT OF

oro-pharyngeal infections

'PONDETS'

A unique presentation of penicillin for the treatment of minor superficial oro-pharyngeal infections.



The ingenious and novel method of presenting penicillin in 'Pondets,' enables a high therapeutic concentration to be maintained in the immediate vicinity of the oro-pharyngeal mucosa, for a prolonged period.

Each 'Pondet' contains 5,000 units of crystalline penicillin-G in a pleasantly flavoured, hard, fruit-sweet base, which dissolves slowly in the mouth.

'Pondets' are indicated for all minor superficial oral infections due to penicillin sensitive organisms.

WINGS DAY SEPT 20th Give for those who Gave

Individually wrapped in bottles of 20.

'Pondets' *Trade Mark* **PENICILLIN TROCHES**

Wyeth

JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1

THERE'S STRENGTH IN COMBINED ACTION

The answer to many a problem lies in combined action. Witness the higher blood levels and the greater clinical efficacy that have been reported from the oral administration of penicillin and the sulphonamides simultaneously in cases when the oral administration of the antibiotic or chemotherapeutic agent alone has been ineffective. A convenient means of applying this combined antibacterial therapy is Sulpenin. Containing penicillin, sulphadiazine and sulphamerazine in balanced dosage, it provides a valuable treatment for many infections due to susceptible micro-organisms. By utilising the synergistic action between penicillin and the sulphonamides the antibacterial range is increased, the likelihood of kidney damage is lessened and the tendency for the bacteria to develop mutant strains resistant to one or other of the component drugs is reduced.

SULPENIN

Combined Oral Penicillin and Sulphonamide Therapy

In tubes of 10 and bottles of 100 tablets.

Literature and Samples on request.

ALLEN & HANBURYS LTD LONDON E 2

TELEPHONE BISHOPSGATE 3201 (17 LINES) TELEGRAMS "GREENBURYS BETH LONDON"

BY THE ORAL AND INTRAMUSCULAR ROUTES...

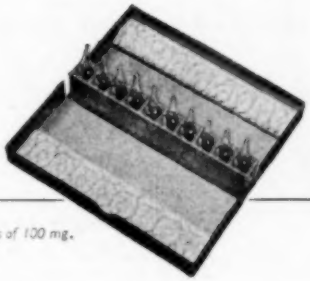
Recent studies have confirmed the value of khellin in

BRONCHIAL ASTHMA
WHOOPING-COUGH
CHRONIC COR PULMONALE
ANGINA PECTORIS

Benecardin

Trade Mark

Benecardin is a potent bronchial relaxant and coronary dilator. Unlike such drugs as glyceryl trinitrate and aminophyllin its effect is cumulative, resulting in a sustained response. It has no action on the systemic vessels and, therefore, does not affect the blood pressure.



Ampoules of 100 mg.

Tablets of 25 mg.

Further information is obtainable from: **Benger Laboratories**

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE · ENGLAND

Thank you, doctor!

Auralgicin TRADE MARK **for the**

relief of pain in acute otitis media

—particularly in children

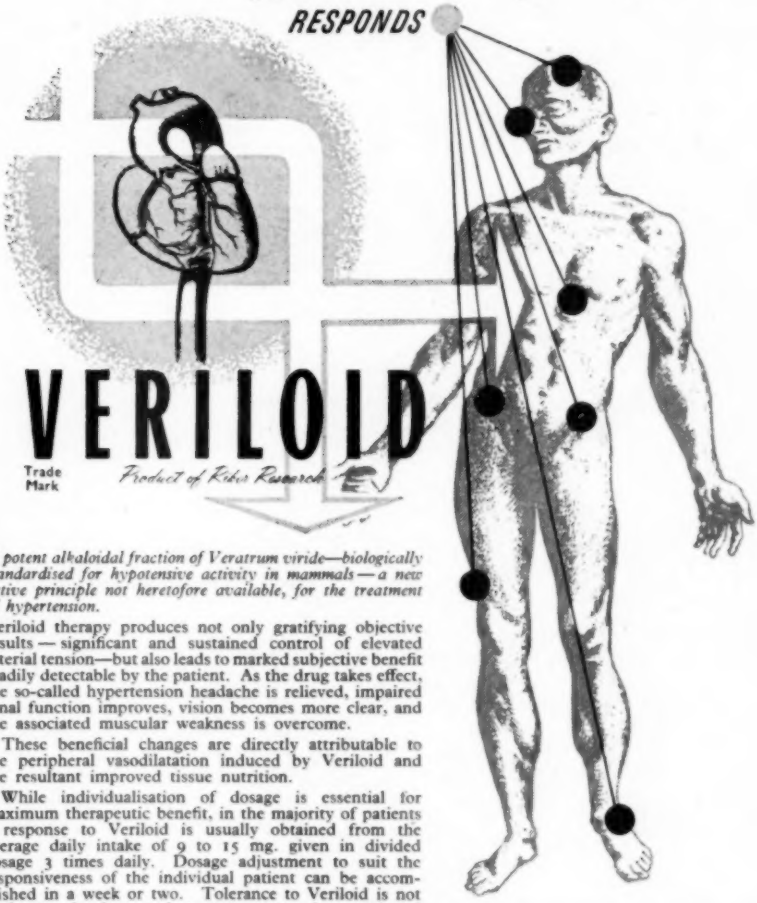
Benger Laboratories

In acute ear infections, few drugs are effective owing to their inability to reach the site of infection. By selecting an antibacterial substance with a wide spectrum of activity and combining it with agents which decongest, promote drainage and reduce discharge, this difficulty is overcome. Auralgicin ear drops were designed for this purpose—they have proved particularly effective.

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE · ENGLAND

The Hypertension Syndrome

RESPONDS



VERILOID

Trade Mark

Product of Riker Research

A potent alkaloidal fraction of Veratrum viride—biologically standardised for hypotensive activity in mammals—a new active principle not heretofore available, for the treatment of hypertension.

Veriloid therapy produces not only gratifying objective results — significant and sustained control of elevated arterial tension—but also leads to marked subjective benefit readily detectable by the patient. As the drug takes effect, the so-called hypertension headache is relieved, impaired renal function improves, vision becomes more clear, and the associated muscular weakness is overcome.

These beneficial changes are directly attributable to the peripheral vasodilatation induced by Veriloid and the resultant improved tissue nutrition.

While individualisation of dosage is essential for maximum therapeutic benefit, in the majority of patients a response to Veriloid is usually obtained from the average daily intake of 9 to 15 mg. given in divided dosage 3 times daily. Dosage adjustment to suit the responsiveness of the individual patient can be accomplished in a week or two. Tolerance to Veriloid is not likely to develop, and treatment can be continued indefinitely without deleterious effect.

Veriloid is available on prescription only through all pharmacies in 1 mg. and 2 mg. tablets in bottles of 100 and 500. Literature available on request.

RIKER LABORATORIES LTD.,
29, KIRKEWHITE STREET, NOTTINGHAM

Veriloid is also available as Veriloid-VP, containing Veriloid 2 mg. and Phenobarbitone B.P. 15 mg. for administration to patients who find it difficult to tolerate Veriloid alone.
For injection in cases of hypertensive crises, it may be obtained in ampoules containing Veriloid 0.4 mg. per c.c. in 0.25% acetic acid, under the style of Veriloid Intravenous Solution.

MACFARLAN'S
ANAESTHETIC
ETHER (Keith's)

Those who have used it know the purity and reliability of this anæsthetic agent, the result of nearly a century of patient research and experience.

Samples are available on request.

J. F. MACFARLAN & CO. LTD.

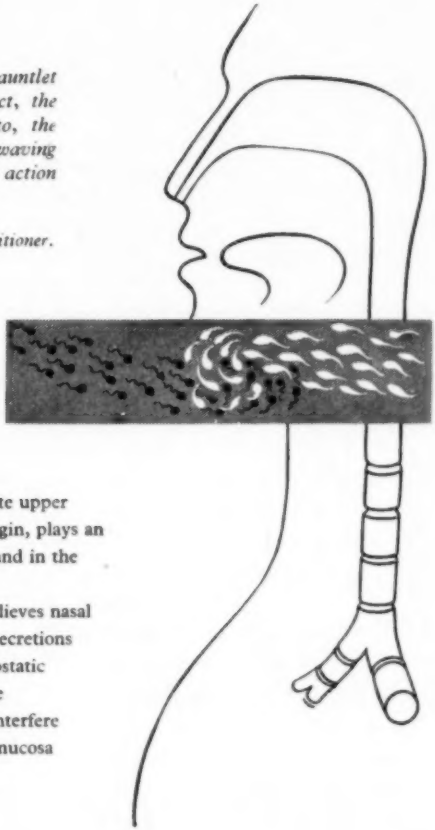
ESTBD. 1780

109 ABBEYHILL
EDINBURGH, 8

8 ELSTREE WAY
BOREHAM WOOD
HERTS.

'. . . a germ successfully running the gauntlet of the intricacies of the upper air tract, the mucus spread out for it to adhere to, the phagocytes in readiness to slay it, and the waving armies of ciliated epithelium in constant action to expel it . . .'

, *Practitioner*.
1901, **67**, 83



'Sulfex', administered intranasally in acute upper respiratory-tract infections of bacterial origin, plays an important part in the relief of symptoms and in the control of infection.
The vasoconstrictive action of 'Sulfex' relieves nasal obstruction and permits free drainage of secretions from the affected sinuses, and the bacteriostatic action of the 'Mickraform' crystals of free sulphathiazole inhibits the bacteria that interfere with the restoration of the infected nasal mucosa to a normal physiological condition.

acute upper respiratory-tract infections respond to . . . .

intranasal 'SULFEX'

An aqueous suspension of microcrystalline ('Mickraform') sulphathiazole, 5%, in an isotonic solution of 'Paredrine', 1% (pH 5·5 to 6·5.) Issued in 1-oz. bottles.

MENLEY & JAMES, LIMITED, COLDHARBOUR LANE, LONDON, S.E.5
for *Smith Kline & French International Co., owner of the trade marks 'Sulfex', 'Mickraform', & 'Paredrine'*
SXP52

An Effective Antacid

of established value

Immediate neutralization of gastric acid, yet unaccompanied by the disadvantages arising from carbonate medication, clearly indicates the clinical superiority of 'Milk of Magnesia'* as a therapeutic antacid.

Non-systemic in action, 'Milk of Magnesia' may confidently be prescribed in a wide variety of conditions associated with gastric acid disturbance—from the mild case of dyspepsia to the acute ulcer stage—where intensive alkaline treatment is essential.

'Milk of Magnesia' reacts with the acids of the stomach to form a neutral laxative salt which promotes gentle but effective elimination.

'Milk of Magnesia'

REGD.

ANTACID LAXATIVE

The Chas. H. Phillips Chemical Co. Ltd.

1, WARPLE WAY, LONDON, W.3.

* *'Milk of Magnesia' is the trade mark of Phillips' preparation of magnesia.*

ULCER CHARACTERISTICS

Deep Naso-Labial Groove

WINGS DAY
SEPT 20th
Give for those who Gave

Clinicians have repeatedly noted a similarity of facies in patients suffering from peptic ulcer, the outward signs of an inward worrying character part cause and part effect of the ulcer. The deep naso-labial groove or furrow is an example of one of the features commonly seen in these cases. While by itself of no diagnostic significance it is nevertheless an interesting little link in the chain of evidence that leads from suspicion to certainty. A more reliable characteristic of the ulcer patient is amenability to 'ALUDROX' therapy.

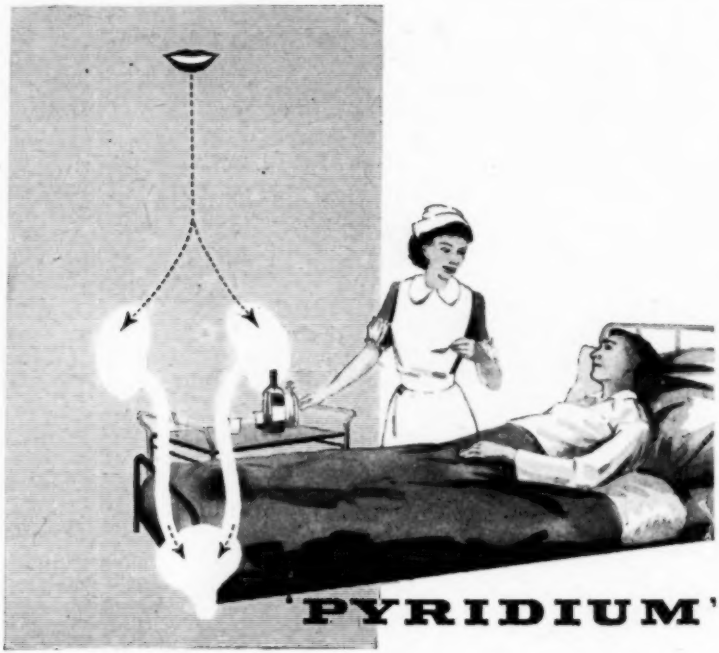
'ALUDROX' FOR PEPTIC ULCER

For the treatment of peptic ulcer 'ALUDROX' has advantages now fully appreciated by the medical profession.

* Buffers gastric acid.
* Inactivates pepsin.
* No acid rebound.
* No fear of alkalosis.
* Allows normal digestion to proceed.

'Aludrox'
Trade Mark

Wyeth JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, N.W.1



'PYRIDIUM'

for Urogenital Analgesia

'Pyridium' by mouth produces local analgesia of the urogenital mucosa — often within thirty minutes of the first dose. Distressing urinary symptoms such as pain, frequency, and strangury, which occur in most cases of infection or irritation of the urinary tract, are rapidly relieved by the administration of 'Pyridium'. 'Pyridium' does not hinder investigation of the pathology of the condition, nor interfere with the institution of specific therapy after the cause of the symptoms has been elucidated.

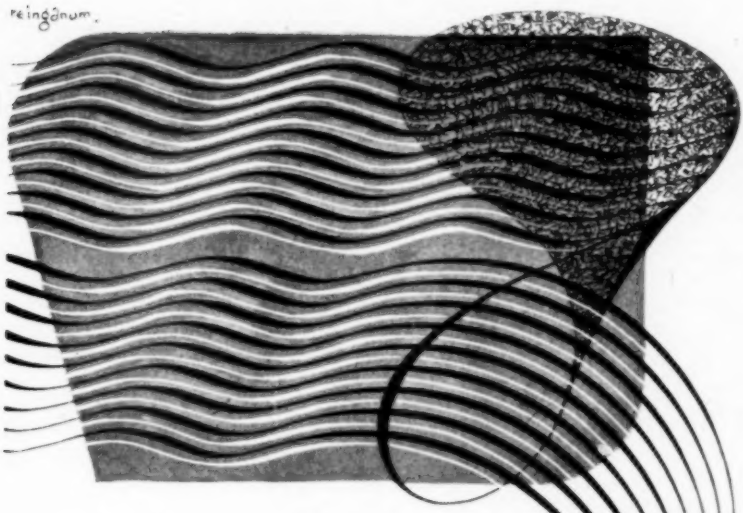
'PYRIDIUM' tablets

Samples and literature on request

'Pyridium' is the registered trade mark of Nepera Chemical Co., Inc., to designate its preparation of phenyl-azo-α-α-diamino-pyridine hydrochloride

MENLEY & JAMES, LIMITED, COLDHARBOUR LANE, LONDON, S.E.5

L...52



For even greater security in Sulphonamide Therapy

'*Cremotresamide*' reduces the incidence of crystalluria — the primary factor causing renal complications in patients undergoing sulphonamide therapy. '*Cremotresamide*' is particularly acceptable to children, but will be found useful in all age groups.

'*Cremotresamide*' contains 0.5 G. of the mixed sulphonamides in each teaspoonful — Sulphadiazine 0.2 G., Sulphamerazine 0.1 G., Sulphacetamide 0.2 G.

SHARP DOHME

Descriptive literature, clinical package and dosage card gladly forwarded on request.

Sharp & Dohme Ltd., Hoddesdon, Herts.

'Cremotresamide'

Trade Mark

Triple Sulphonamide Suspension

New Peptic Ulcer Treatment Comparable to Drip Therapy

Whole milk and alkaline constituents combine to produce increased buffering action

NULACIN TABLETS have been evolved to meet a very real need in the treatment of gastric and duodenal ulcers.

All the literature on the treatment of peptic ulcers emphasizes the proven value of diminishing the acidity of the gastric juice. Many large and otherwise intractable ulcers can be healed by a continuous, intragastric drip of milk or alkali.

Drip therapy is, however, not always available, nor is it practicable to use it in many instances. Nulacin offers a satisfactory alternative.

Continuous Neutralization

A NULACIN TABLET allowed to dissolve slowly in the mouth has been shown clinically to provide a continuous neutralization comparable with that of drip therapy.

NULACIN TABLETS contain nutrient in a most acceptable form to the peptic ulcer patient. Nulacin tablets obviate the necessity of taking frequent feeds, and so lessen the tendency to obesity which must inevitably occur in those who are following a dietary regime of food at frequent intervals.

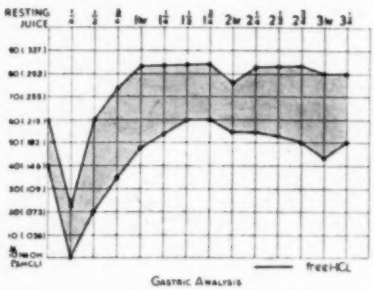
During ulcer activity the suggested dosage is 3 tablets to be sucked each hour, and for follow-up treatment 2 tablets should be sucked between meals, beginning half an hour after a meal.

The tablet is of a suitable size, and of a consistency and hardness, so that, when it is sucked, the result is a constant and prolonged neutralization of the gastric juice.

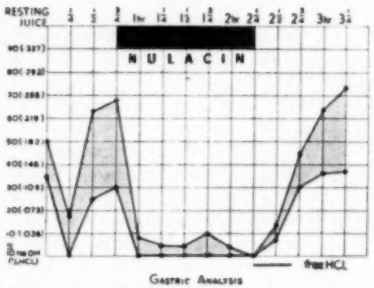
NULACIN TABLETS are extremely palatable and during extensive clinical tests their taste has proved to be particularly acceptable to patients.

The patient should be instructed to place the tablet between the gum of the upper jaw and the cheek. Here it will be comfortable, and slowly dissolve. The efficacy of the tablet is greatly diminished if it is chewed and swallowed.

NULACIN TABLETS are not advertised to the public. There is no B.P. equivalent to this tablet.



Superimposed gruel fractional test-meal curves of five cases of duodenal ulcer.



The same patients as in Fig. 1, two days later, showing the striking neutralizing effect of sucking Nulacin tablets (3 an hour). Note the return of acidity when Nulacin is discontinued.

NULACIN TABLETS are prepared from whole milk combined with dextrins and maltose, and incorporate:

Magnesium Trisilicate 3.5 grs. Magnesium Oxide 2.0 grs. Calcium Carbonate 2.0 grs. Magnesium Carbonate 0.5 grs. Ol. Menth. Pip. q. s.

NULACIN TABLETS are at present packed in bottles of 100 and tubes of 12.

NULACIN

HORLICKS LIMITED

PHARMACEUTICAL DIVISION, SLOUGH, BUCKS.

The dual action of 'Edrisal' can produce a dramatic change in the picture presented by the rheumatic patient. It effectively relieves not only the pain but also the depression so often associated with 'rheumatic' pain.

anti-rheumatic therapy

This improvement in mood is of outstanding value in a disease where the influence of the mind over the body is so marked. It beneficially alters the reaction to pain and lessens the patient's preoccupation with his symptoms. Dose: 2 tablets repeated three hourly as necessary.

'Edrisal' *the dual-action analgesic — relieves pain — elevates mood*

Available on prescription in bottles of 25 tablets

Each 'Edrisal' tablet contains:
Amphetamine ('Benzedrine') sulphate . . . . . 2·5 mg.
Acetylsalicylic acid . . 160 mg.
Phenacetin . . . 160 mg.

MENLEY & JAMES, LIMITED, COLDHARBOUR LANE, LONDON, S.E.5

for Smith Kline & French International Co., owner of the trade marks 'Benzedrine' and 'Edrisal'

FAP92

How to reduce the 'Time-Lag' in the treatment of Rheumatism

Despite half a century of painstaking research, there is still no unanimity of opinion regarding the causation of rheumatic diseases. Treatment is therefore necessarily symptomatic and directed to the relief of pain.

Massage has long been the treatment of choice. But in severe cases adequate massage cannot as a rule be begun at once; the affected muscles are too taut and tender. Days or even weeks may have to elapse before the patient can benefit from the stimulating effects of deep massage.

This 'time-lag' has now been eliminated by the use of Lloyd's Adrenaline Cream.

Gentle massage over the affected myalgic spots with this cream brings rapid relief from pain and permits of more intensive treatment than would otherwise be possible.

Supplies of Lloyd's Adrenaline Cream are now available through Boots, Timothy Whites & Taylors, and all pharmacists.

Howard Lloyd + Co. Ltd.

11 Waterloo Place, London, S.W.1

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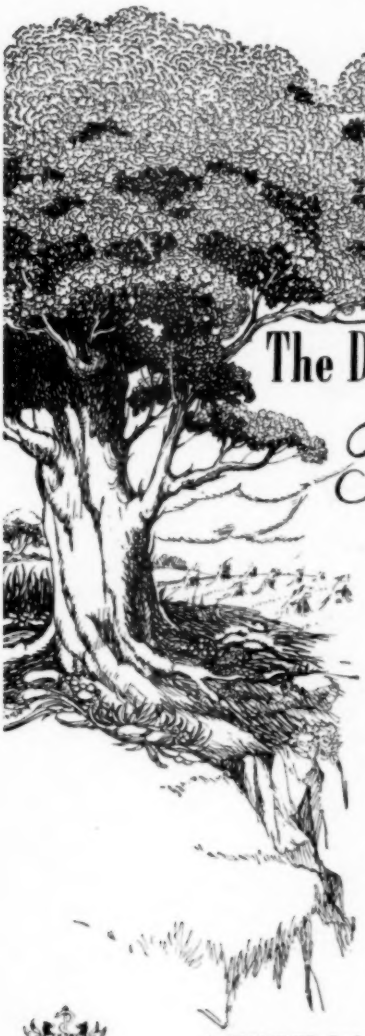

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THE PRACTITIONER

No. 1011 SEPTEMBER 1952 Volume 169

THE MONTH

The Symposium

ENDOCRINOLOGY, at one time the happy hunting ground of the 'also-rans' of medicine, has, during the last three decades, developed into one of the major branches of medicine, and there are good reasons for believing that developments in this field may produce some of the greatest advances in our knowledge of disease processes during the coming years. In our symposium this month priority is given to the two aspects of the subject which have aroused greatest interest during recent years—cortisone and ACTH. There has been a natural tendency for these two important hormones to be associated with the rheumatic group of diseases. Now that the initial excitement surrounding the momentous observations of the Mayo Clinic workers three years ago is settling, there is a general realization of the important rôles cortisone and ACTH play in the normal and abnormal processes of the body. It is these general attributes which are reviewed by Professor L. J. Soffer and Professor F. G. Young. Thyrotoxicosis is one of the most common of the endocrine dysfunctions, and any discussion of its treatment can be guaranteed to produce a lively difference of opinion as to the relative merits of surgery and drugs. In his article on 'the treatment of thyrotoxicosis' Dr. Raymond Greene provides a judicial summing up of the present status of the various forms of therapy. Although the œstrogens and the androgens are among the most widely used of the hormones, there is still considerable confusion in the practitioner's mind as to their precise indications. Their present clinical status is reviewed by Mr. R. K. Bowes and Dr. A. C. Crooke respectively. To reduce without dieting is the ambition of most obese individuals. The hope has still to be dashed in most cases. Meanwhile, however, the endocrinological aspects of obesity continue to attract much attention, and these are discussed by Dr. A. W. Spence.

The Prescription Levy

EVEN though the prescription levy, which came into force on June 1, was introduced primarily as one of those stop-gap measures for reducing Government expenditure in which Whitehall has specialized since the end of the war, there were many outside the political arena who welcomed it as a measure which might instil a certain degree of responsibility into the public's attitude towards the National Health Service. A report in the *Pharmaceutical Journal* suggests that the levy is promising to subserve this useful function as well as reduce the N.H.S. expenditure for drugs. The report is based upon a survey of the number of prescriptions submitted

by contractors for payment in June 1951 and June 1952 (the first month of the levy), covering about one-third of the population of England. The areas included in the survey were Bournemouth, Essex, Lancashire, London, Middlesex, Norfolk, Surrey and the West Riding of Yorkshire, and may therefore be taken as representative of the country as a whole. The figures show a percentage reduction in the number of prescriptions dispensed ranging from 18.8 in Lancashire to 10.8 in Surrey. The reduction in the number of forms is even greater: e.g., 19.2 per cent. in Essex and 25.6 per cent. in the West Riding. This disproportion is explained by the increase in the number of prescriptions per form, 'but allowing for this increase the fact emerges that substantially fewer people received prescriptions from their doctors'. Particularly interesting is what has happened in hospitals. 'From reports received from chief pharmacists in a number of widely dispersed teaching hospitals it seems that only a few patients have grumbled. . . . Very few persons have claimed the necessary exemption from the almoners' departments. Patients appear to regard the payment as not unreasonable: perhaps some of them remember a similar charge made for medicines in the former voluntary hospitals, where a flat rate was payable at the dispensary and all other treatment of out-patients was free'. These findings will not satisfy those to whom the present Service is merely a step towards nationalization of the medical profession, but they do suggest that the people of the country are not unwilling to make a direct contribution towards the cost of their medicine, and that the imposition of such a levy does reduce the demands for unnecessary medication. There is no reason why the principle should not be developed, provided always that it is not made an excuse for relaxing control over expenditure in other branches of the Service.

The Medical Curriculum

MUCH lip-service has been paid to reform of the medical curriculum, but there is as yet little evidence that the problem is being tackled in a realistic manner. Much has been added, but little has been taken away, and the result is a state of affairs which is the antithesis of everything for which a university education should stand. The present position is admirably summed up in the current issue of the *University of Edinburgh Journal* in reviewing the new six-years' curriculum for the Edinburgh M.B., CH.B. degrees. In the first or 'pre-medical' year the average requirement of class-attendance is 22 weeks throughout the entire session of three terms—'that is, time spent in sheer instruction, apart from what must be given to his own reading in his subjects'. In the fifth and sixth years the position is even worse: in the former the student is supposed to spend 30 hours a week in classes; 27 hours in his sixth year. On this deplorable state of affairs the Journal comments: 'Every teacher is, naturally and rightly, convinced of the primary importance of his own subject and of his own presentation of it; but the student—who, after all, is supposed to be training himself for the most

responsible of all professions—must in the last resort be left to decide for himself when, what (and whom) to "cut", or how best to apportion the hours of his fearfully crowded days, between listening and watching, reading, and keeping himself physically fit and *mentally alive*' (the italics are ours). The position may not be quite so serious in the London Medical Schools, but there is the same tendency to fill up every moment of the student's time. The modern medical curriculum has degenerated into a highly technical training which may produce efficient laboratory workers and fillers-up of forms. It will certainly not produce educated men and women with an understanding of human nature, the ability to think, and a love of freedom and independence of thought. As a training for a nationalized medical service in a totalitarian State this may be the right course, but it spells the end of all those traditions upon which the glory of the medical profession has rested in the past. The tragedy of the whole situation is that those responsible for the government of our Universities are either unwilling, or unable, to see the devastating effect upon the standards of medical practice.

Cancer Propaganda

THE fact that the 'problem of greater publicity in the matter of cancer treatment' should have been the subject of debate recently in the House of Commons indicates the widespread interest there is in the matter. The reasons for this interest are not far to seek. Cancer is now one of the major killing diseases; it is a disease which is dreaded by the public because of its reputation for killing; there has been much propaganda from the medical profession that early diagnosis may mean successful treatment; the cause, and therefore specific therapy, are still eluding us. Perhaps a more direct cause for the matter being raised in Parliament—incidentally, a most unsuitable place for a discussion on the subject—was the resurgence in the medical and lay press of pleas by certain members of the profession for more intensive propaganda to encourage potential victims of the disease to report to their doctors at an earlier stage than they do at the moment.

Unfortunately, the 'data' upon which much of this agitation for education of the public in cancer is based are anything but conclusive. As Professor N. E. McKinnon of Toronto has recently pointed out (*British Medical Journal*, July 19, 1952, p. 158), 'After all allowance is made for the frailties of vital statistics, the maintenance of uniform levels in age-specific breast cancer mortality rates over 20-25 years in areas with and without "control" programmes, with and without the provision of extensive diagnostic and treatment facilities, with and without cancer "education", and with and without demonstrated shifts to early treatment shows clearly, without questionable assumptions or ambiguity, that such early treatment failed to prevent any appreciable amount of mortality'. It is typical of the confusion of thought on the subject that it was only a few days after this opinion was published that the statement was made in the House of Commons that

secrecy . . . is condemning thousands of people to die many years before they need'. Incidentally, it is interesting to note that, in discussing the commonly held view among doctors that propaganda concerning cancer might cause undue apprehension in the public, the distinguished back-bencher who raised the matter for discussion should have added 'In any case, we have so much to be apprehensive about in this particular day and generation that one more cause of apprehension can hardly prove fatal to our morale'. As the Parliamentary Secretary to the Ministry of Health pointed out, 'it would be wrong to have a national campaign based on fear', and with the best intentions in the world, any public campaign on cancer would inevitably be based, fundamentally, on fear. The Ministry of Health Standing Cancer and Radiotherapy Advisory Committee is right in its advice against a cancer campaign addressed direct to the public. Until an effective form of treatment is discovered, it is the duty of the medical profession to support this decision. In the present state of our knowledge the early diagnosis of cancer is the duty and responsibility of the doctor—not the patient.

Royal Medical Society

EDINBURGH is justly proud of the Royal Medical Society—the oldest medical society in Great Britain. It was formally constituted in 1737, and incorporated by Royal Charter in 1778. Its bicentenary was celebrated with due ceremony in 1937, but it is only now that the history of these two hundred years has been published ('History of the Royal Medical Society 1737-1937'. By James Gray. Edited by Douglas Guthrie, M.D., F.R.C.S.ED. Edinburgh: The University Press, 1952. Price 42*s*.). Characteristically Scottish in its eclectic approach to medicine, its roll of members has included names famous in many spheres other than medicine: e.g. Oliver Goldsmith, Sydney Smith, Charles Darwin, Lord Geddes. In the field of medicine its members have included practically all the outstanding members of the Edinburgh School of Medicine and many who distinguished themselves elsewhere, such as Astley Cooper, Thomas Addison, Richard Bright, Thomas Hodgkin, and Burdon-Sanderson. What is perhaps not so well known is the close association between the Society and the first medical faculty in America—the faculty of the University of Pennsylvania. John Morgan, the first professor of practice of physic; Benjamin Rush, who was appointed professor of the institutes of medicine when the Medical College of Philadelphia was incorporated into the University of Pennsylvania; and Caspar Wistar, who was appointed professor of anatomy in the University of Pennsylvania in 1791, and whose name is perpetuated in the Wistar Institute of Philadelphia, were all members. The Society's history is packed with incident, including a president killed in a duel in 1789. It has had its vicissitudes, but throughout the centuries it has maintained its reputation for providing the medical students of Edinburgh with a forum in which they could develop that freedom of speech, skill in dialectics and respect for logic which have for long been the hallmark of the Scottish universities.

CORTISONE: A REVIEW OF THE PRESENT POSITION

By LOUIS J. SOFFER, M.D., F.A.C.P.

Associate Attending Physician and Head of the Department of Endocrinology, The Mount Sinai Hospital, New York City; Assistant Clinical Professor of Medicine, Columbia University.

In March, 1936, at a meeting of the American Society of Biological Chemists, Kendall, Mason, Myers and Allers[1] reported the isolation from beef adrenal extracts of 17-hydroxy-11-dehydrocorticosterone (Compound E). At this same meeting Pfiffner and Wintersteiner[2], entirely independently, presented a preliminary report concerning a similar fraction which they referred to as 'Substance F', which was apparently identical with the 'Compound E' of Kendall and his co-workers. The preliminary studies on this fraction reported by Pfiffner and Wintersteiner were not so far advanced as those reported by Kendall and his associates. In April, 1936, Mason, Myers and Kendall[3] submitted a paper for publication in the *Journal of Biological Chemistry*, in which they reported the isolation in crystalline form of 'Compound E' and found it to be in agreement with the formula $C_{21}H_{38}O_5$. Subsequently, they revised the formula to the presently accepted one of $C_{21}H_{28}O_5$. In July, 1936, Wintersteiner and Pfiffner[4] submitted to the same journal a report on the 'isolation of 2 new physiologically inactive compounds', one of which was 'Compound F' corresponding to Kendall's 'Compound E'. In this report the authors claimed that this fraction constituted the bulk of the 'chloroform insoluble crystals' obtained from their fractions 10 and 11 previously reported.[5,6] During this same year Reichstein[7] isolated 'Substance Fa', which he showed to be identical with 'Compound E' of Kendall and 'Compound F' of Wintersteiner and Pfiffner. Subsequently, Steiger and Reichstein[8] established the structure of these three identical fractions as pregnene-4-diol-17 (β), 21-trione-3,11,20. In 1946, Sarett[9] described the partial synthesis of 'Compound E' from desoxycholic acid. The term 'cortisone', which was introduced by Kendall, serves to eliminate the confusion associated with the use of different letters ascribed to this fraction by the various investigators.

The next step in the development of this field was the demonstration by Hechter and his associates[10] of the biological oxygenation of 11-desoxycorticosterone at C-11. These investigators found that the perfusate resulting from the perfusion of 11-desoxycorticosterone through isolated cow adrenal glands contained considerable glycogenic activity. Further work resulted in the isolation from these perfusates of corticosterone (Compound B), which was apparently the principal crystalline transformation product. Quite independently, Hayano, Dorfman and Prins[11], using adrenal slices and an adrenal homogenate preparation, also demonstrated the conversion of 11-

desoxycorticosterone into material possessing glycogenic properties. In subsequent studies Hechter and his associates,[12] employing the original cow adrenal perfusion techniques, and McGinty and his group,[13] using adrenal homogenates similar to the technique of Hayano and his co-worker,[11] demonstrated the biological conversion of 17-hydroxy-11-desoxycorticosterone (Compound S) into 17-hydroxycorticosterone (Compound F). According to Hechter, adrenal perfusion with 11-desoxycorticosterone results in the formation *only* of corticosterone, whilst with 17-hydroxy-11-desoxycorticosterone (Compound S) *only* 17-hydroxycorticosterone (Compound F) is formed.

These studies represent the first demonstration of the biological oxygenation at C-11 of certain adrenal steroids, thus altering the metabolic effects of the original fractions. More recently Peterson and Murray[14] reported the microbiological oxygenation of steroids at C-11, using fungi of the order of 'mucorales', whilst Colingsworth, Brunner and Haines[15] described the conversion of 'Compound S' to 'Compound F', and of desoxycorticosterone to corticosterone (Compound B) by microbiological oxygenation at C-11, employing *Streptomyces fradiæ*, Waksman's strain 3535. It is of considerable potential practical significance, not only in regard to the manufacture of Compounds B and F, but also of cortisone, that such oxygenation can occur entirely independently of the adrenal.

PHYSIOLOGICAL AND METABOLIC CONSIDERATIONS

The factors concerned with the elaboration of the adrenal cortical steroids are by no means entirely clear, but at least two processes are of considerable importance: (1) the discharge of adrenaline into the circulation, and (2) the level of the circulating adrenal cortical hormones. When an organism is subjected to alarm or stress, a series of responses occurs, characterized essentially by an increase in the function of the adrenal cortex resulting from the discharge of corticotrophin (ACTH) by the adenohypophysis.[16] These phenomena are similar to those observed in the experimental animal following parenteral administration of both adrenaline[17] and corticotrophin.[18] Whether adrenaline actually causes an increase in the elaboration of corticotrophin from the adenohypophysis, or whether its effect is exerted directly on the adrenal or on the increased utilization of adrenal cortical steroids by the peripheral tissues, is a subject of a good deal of debate at present.[19] The parenteral administration of adrenaline, however, does result in increased secretion of thyrotrophic factor from the adenohypophysis.[20,21] The secretion of both corticotrophin and thyrotrophin is inhibited by the administration of cortisone.[21] Following the injection of corticotrophin to both intact and bilaterally adrenalectomized rats there occurs a significant decrease in the collection of I^{131} by the thyroid gland of both groups of animals.[21,22] This effect may be due to an actual inhibition of secretion of thyrotrophin, or it may represent an interference with the ability of the thyroid gland to utilize thyrotrophin,[23,24] or perhaps a combination of several

factors. These phenomena are by no means limited to the experimental animal. Subsequent clinical studies concerning the influence of cortisone on the thyroid collection of tracer doses of I^{131}, and on the level of serum protein-bound iodine in euthyroid and hyperthyroid patients, revealed a decrease in the uptake of radioactive iodine and a reduction of the protein-bound iodine in both groups of patients.[25,26,27] Finally, following surgical stress there often, although not always, occurs an increase in the urinary excretion of gonadotrophins.[28] It is of some interest that the prolonged treatment of patients with either corticotrophin or cortisone is often associated with an increase in the titre of the urinary gonadotrophins.[29]

As a result of these observations the concept of the pituitary-adrenal relationship must be expanded to include the thyroid, and this triangular axis is concerned with response to alarm or stress. A stress situation is therefore characterized by the stimulation of the adenohypophysis, either directly or through the hypothalamus, to the elaboration of both corticotrophin and thyrotrophin. Both fractions stimulate their respective target glands, resulting in the secretion of their hormonal products. The continued effect of corticotrophin is then inhibited by cortisone and similar adrenal cortical fractions, and that of thyrotrophin by cortisone, by corticotrophin, and by the thyroid hormone elaborated by the thyroid gland. In view of the clinical studies already mentioned it is possible that the gonads, too, participate in this general phenomenon.

The physiological and metabolic effects of cortisone differ considerably from those of other adrenal cortical fractions. Desoxycorticosterone-like fractions, and perhaps to a lesser extent Compound S, are concerned primarily with electrolyte and water metabolism, and exercise no effect on carbohydrate metabolism. Both cortisone and Compound F influence protein and carbohydrate metabolism, and perhaps indirectly fat metabolism. The influence of cortisone on electrolyte and water balance is variable, and when this fraction does cause salt and water retention its effect is approximately 1/50 that of desoxycorticosterone. In such circumstances fluid retention is associated with a decrease in the urinary excretion of sodium, an increase in the serum sodium level, a decrease in the serum potassium, and an increase in the urinary excretion of this cation. This is sometimes associated with an increased urinary diuresis of chlorides and the development of hypopotassæmic, hypochloræmic alkalosis. The development of alkalosis during prolonged treatment with cortisone is significant, because it implies a decrease in the body potassium stores. Such depletion in body potassium, however, is not always reflected in a reduction in the serum potassium level.

EFFECT ON WATER METABOLISM

The salt-retaining effect of cortisone is by no meaans a consistent phenomenon. In the experimental animal Thorn and his group[30] and Ingle and Thorn[31] demonstrated in acute experiments in the rat that the administration of

cortisone and Compound F resulted in a temporary increase in the urinary excretion of sodium, chloride and potassium. Apparently similar results are sometimes observed in the dog.[32] In patients, Sprague and his co-workers[33] found that after the administration of 100 mg. of cortisone acetate daily no appreciable change in the balances or serum concentrations of sodium, chloride and potassium occurred. With double this dosage, however, they observed a negative potassium balance, often a retention of sodium and chloride, and occasionally a hypopotassæmic hypochloræmic alkalosis. Levitt[34,35] demonstrated a significant finding in patients on a low-salt diet (8.5 milliequivalents of sodium per day) receiving cortisone or corticotrophin. Using inulin as a measure of extracellular space, he observed a considerable increase after the administration of these agents. This increase in extracellular fluid was not associated with a gain in weight and could not therefore be attributed to excessive exogenous fluid intake. This augmentation in extracellular fluid reached a peak on the eighth or ninth day, and was then followed by a spontaneous reduction in the extracellular space, regardless of whether therapy with the hormonal agents was continued or stopped. The reduction in inulin space was only in part associated with an increased urinary excretion of sodium and water. During the phase associated with an increase in the inulin space there occurred concomitantly a considerable increase in the glomerular filtration rate, little change in the renal plasma flow, and a resultant significant augmentation in the filtration fraction.

In our clinical and experimental experience the influence of cortisone on electrolyte and water metabolism is variable. In some instances fluid retention with œdema occurs with a decrease in the urinary excretion of sodium, and with or without an elevation in the serum concentration of this cation. In others, no change either in water or electrolyte concentrations in both blood and urine is noted. In certain circumstances a urinary diuresis may follow the prolonged administration of cortisone, such as is often observed in the nephrotic syndrome. It is of interest to note that the inadequate diuresis which follows water loading in patients with Addison's disease or hypopituitarism is promptly restored to relatively normal levels following administration of cortisone.[36,37,38,39]

The clinical factors which determine the nature of the electrolyte and water response following the administration of cortisone are by no means clear. Apparently the degree of hydration of the experimental animal or patient plays a considerable part in determining the character of the response. The œdematous patient is less likely to show fluid and sodium retention, except as a transient phenomenon, following the administration of this steroid fraction than is the dehydrated individual. A second factor of considerable importance is the salt intake during therapy. Sharp reduction in the daily sodium intake will limit fluid retention, and will often precipitate a diuresis. Finally, the duration of treatment to some extent determines the influence of this hormone on water and electrolytes. Not un-

commonly the retention of fluid which may promptly follow upon the administration of cortisone is succeeded by a diuresis with the more prolonged administration of the hormone, particularly if the daily sodium intake is reduced to the barest minimum.

When we examine these several experimental and clinical factors it would appear that alterations in the extracellular concentration of sodium and water determine, at least in part, the influence of cortisone on electrolyte and fluid balance. Varying degrees of diuresis will follow when the increase in the glomerular filtration rate and augmentation of the filtration fraction exceed the rate of renal tubular reabsorption of water and electrolytes. The factors which determine the resorptive capacity of the renal tubular cells are obscure. It is possible that the changes in the extracellular compartment directly influence this function of the tubular cells. Recently it has been suggested that this effect may be mediated through the release or suppression of a hypothetical diuretic principle or changes in concentration of the posterior pituitary antidiuretic factor.

EFFECT ON CARBOHYDRATE METABOLISM

The adrenal cortex plays a very considerable part in carbohydrate metabolism. As early as 1927, Cori and Cori[40] showed that fasting adrenalectomized rats had very little liver glycogen. When relatively potent adrenal cortical extracts became available, Britton and Silvette[41] observed that the depleted glycogen stores could be restored to normal by the administration of the extract. Long, Katzin and Fry[42] found, in addition, that adrenal cortical extract could prevent glycogen depletion of the liver in fasting adrenalectomized rats and mice. This was associated in both the intact and adrenalectomized animals with a parallel increase in the urinary excretion of nitrogen. Since the increase in liver glycogen did not come from an exogenous source of glucose, and since it was accompanied by an increase in the urinary excretion of nitrogen, it was reasonable to assume that the breakdown of proteins was responsible for the gluconeogenesis. When cortisone became available for experimental study it was found that this fraction, as well as several others of the 11-oxygenated adrenal cortical steroids, increased the urinary excretion of both glucose and nitrogen in the phlorhizin-induced diabetes of adrenalectomized fasting rats. This was attributed to the anti-anabolic and catabolic effects of the 11-oxygenated steroids on protein metabolism, which thus increased the availability of amino-acids for formation of glycogen and glucose. In addition, it is likely that cortisone causes further changes in carbohydrate metabolism by interfering with the peripheral utilization of glucose.[31,44,45]

Cortisone and Compounds B and F readily induce glycosuria in normal intact rats,[46,47] but in humans such hyperglycæmia and glycosuria are much less consistently observed. In Addison's disease, cortisone often elevates the blood sugar level and decreases glucose tolerance,[48,49,50] and in diabetes mellitus the insulin requirements are considerably increased.[51]

In other groups of patients, however, elevations in the fasting blood sugar levels and decreases in glucose tolerance are only rarely observed.[33,34] In this regard the therapeutic use of cortisone does not constitute a significant clinical problem, except in those patients who are diabetic or potentially so. The exaggeration of the diabetes which occurs in such circumstances requires increased amounts of insulin for control, but with reduction in the dosage of cortisone the insulin requirements become progressively less, and with discontinuance of steroid therapy entirely, the patient promptly reverts to the pre-treatment stage. A transitory ketonuria has been reported in occasional patients receiving cortisone[50], and in the diabetic receiving this fraction there may occur a considerable increase in the urinary excretion of ketone bodies.[52]

EFFECT ON CALCIUM, PHOSPHORUS AND PROTEIN METABOLISM

The influence of the adrenal cortical steroids on the metabolism of calcium and phosphorus and protein is of considerable clinical importance. For the formation of bone, calcium is deposited in a bony matrix which is essentially protein in character. Albright[53] long ago postulated that the osteoporosis observed in Cushing's syndrome was in part due to the reduction in the protein bony matrix, and suggested that the 11-oxygenated steroids of the adrenal cortex exercise an anti-anabolic effect. In the experimental animal Clark,[54] using tracer doses of glycine labelled with N^{15}, found that after the administration of cortisone there occurred a marked increase in the urinary excretion of nitrogen. This was associated with an increased urinary excretion of the radioactive isotope, suggesting that the steroid suppressed protein synthesis from the amino-acid. Hoberman,[55] similarly working with isotopic glycine in the rat, observed that cortisone both increased the rate of protein catabolism and interfered with the conversion of amino-acids to proteins. In patients, various groups [50,33,56] have demonstrated that larger doses of cortisone and corticotrophin will induce a negative nitrogen balance. The concomitant increased urinary excretion of uric acid and creatine suggests that actual protein breakdown occurs. Finally, Parson,[57] using labelled glycine in human subjects, found that the adrenal steroids exercised an anti-anabolic effect similar to that observed in the experimental animal. It would therefore seem that cortisone and probably other 11-oxygenated adrenal cortical steroids influence protein metabolism in two directions: (1) by suppressing the synthesis of proteins from amino-acids, and (2) by increasing the breakdown of proteins to their constituent amino-acids. The increased availability of amino-acids permits their diversion for gluconeogenesis.

OTHER CHANGES INDUCED BY CORTISONE

A number of changes induced by cortisone are not related to any specific metabolic derangements. In the experimental animal, large doses of cor-

tisone are capable of producing necrotizing lesions in the cardiac and skeletal musculature,[58,59] and pathological changes in the kidney of the unilaterally nephrectomized rat indistinguishable from those of acute glomerulonephritis.[60] On the other hand, it has been reported that excessive amounts of cortisone will inhibit the pathological changes in the heart, kidney, and pancreas, induced by the administration of desoxycorticosterone acetate.[61]

The 11-oxygenated steroids, notably cortisone and Compound F, exercise some effect on the various enzyme systems. These fractions are capable of inhibiting hyaluronidase and lysozyme and increasing the enzymatic effects of pepsin, pepsinogen, uropepsin, serum peptidases, histaminase, and arginase.[62,63,64]

Both cortisone and ACTH have been used successfully in the clinical management of various allergic states, but their precise mechanism of action, however, is unknown. Neither of these fractions inhibits experimental anaphylaxis in the guinea-pig, nor do they affect the passive Arthus phenomenon in guinea-pigs or rabbits.[65] Both ACTH and cortisone, however, inhibit the provocative phase of the Shwartzman phenomenon.[66] Some investigators have reported a reversal of the previously positive tuberculin reaction following the use of cortisone or ACTH[67], but this is by no means a consistently observed phenomenon. Finally, neither ACTH nor cortisone suppresses the formation of streptococcal antibodies in acute rheumatic fever.[68]

CLINICAL CONSIDERATIONS

Cortisone has been widely used in the treatment of disease. Table 1 lists the various illnesses in which it has been reported to exercise some effect. It is almost certain that this compendium by no means exhausts the list. The fact that this fraction is capable of influencing such a large group of ostensibly unrelated disease processes poses the problem of the reason for its effectiveness. There are essentially two possibilities to consider: (1) that these pathological states have in common a disturbance of adrenal cortical function which is fundamentally related to the cause of the disease; (2) that the adrenal cortex simply participates in the general defence mechanism of the body. There is little laboratory evidence to support the first hypothesis, except in those specific endocrine disorders in which the adrenals are overtly involved. It has, however, been suggested that disease in general arises as a result of adaptative mechanisms to stress, a phenomenon in which the adrenals play a fundamental part.[69] Indeed, Selye has enumerated a long list of pathological states having their origin in such a process. There may be some issue as regards the wide spectrum embraced by this author, but there is ample evidence to suggest that this phenomenon does play a part in the development and evolution of certain disease states. It is important to remember that cortisone does not cure those diseases in which it is ostensibly effective. Rather, the rôle of this fraction is a suppressive one in which the

symptoms are held in abeyance, the patient made considerably more comfortable, but the underlying disease process remains essentially unaltered. This would suggest that in most instances, with the exception of those

TABLE I

INDICATIONS FOR THE USE OF CORTISONE AND ACTH

(1) *Effective*
- (A) Life-saving:—
  - (i) Short-term therapy:
    - Severe burns
    - Preoperative preparation for adrenalectomy in patients with adrenal cortical tumour
    - Waterhouse-Friderichsen syndrome
    - Severe serum sickness
    - Severe acute rheumatic fever
    - Severe status asthmaticus not responsive to other therapy
    - Markedly toxic pneumonias or severe systemic infections not responsive to antibiotics
    - Generalized severe peritonitis (in conjunction with antibiotics)
    - Severe exfoliative dermatitis
    - Postoperative intractable shock
  - (ii) Long-term therapy:
    - Acute disseminated lupus erythematosus
    - Periarteritis nodosa
    - Dermatomyositis
- (B) Prevention of morbidity or disability:—
  - (i) Short-term therapy:
    - Acute gout
    - Hay fever
    - Urticaria
  - (ii) Long-term therapy:
    - Rheumatoid arthritis
    - Inflammatory diseases of the eye
- (C) Effective, but not necessarily life-saving:—
  - (i) Short-term therapy:
    - Nephrosis
    - Erythema multiforme
    - Spontaneous idiopathic hypoglycæmia
  - (ii) Long-term therapy:
    - Addison's disease
    - Congenital adrenal hyperplasia
    - Panhypopituitarism
    - Boeck's sarcoidosis
    - Weber-Christian disease

(2) *Equivocal: sometimes but not always effective*
- (i) Short-term therapy:
  - Thyroid storm
  - Severe hepatitis
  - Idiopathic thrombocytopenic purpura (not associated with a hypoplastic bone marrow)
- (ii) Long-term therapy:
  - Ulcerative colitis
  - Regional ileitis
  - Pemphigus
  - Acute leukæmia
  - Berylliosis
  - Acquired hæmolytic anæmia
  - Scleroderma
  - Multiple myeloma
  - Lymphomas
  - Myasthenia gravis
  - Thymic tumours
  - Psoriasis

states resulting from direct and overt involvement of the adrenals, cortisone does not constitute true substitution therapy but rather serves to heighten, in a manner as yet unknown, the defence response to threatening situations and noxious agents. In this sense both ACTH and cortisone are effective in a non-specific way, related to exogenously induced increased adrenal cortical response.

The prolonged use of cortisone is associated with certain hazards which must be borne in mind It may result in the development of a number of clinical manifestations, some of which resemble Cushing's syndrome (table 2). The frequency and character of the complications are in part determined by the nature of the underlying illness, the duration of therapy, and the dosage employed. *Hypertension* occurs more commonly in patients with underlying renal or vascular disease than in those groups free from these defects. It is for this reason that it is so much more often encountered during therapy in patients with acute disseminated lupus erythematosus or periarteritis nodosa than in individuals with rheumatoid arthritis or asthma. Hypertension, when it occurs, is not a permanent feature, and the blood pressure reverts to the pre-treatment level when the use of the steroid is discontinued or the dosage reduced. Restriction in the daily sodium intake plays a comparatively minor part either in the prevention or the control of this complication. Œdema and heart failure, on the other hand, can be successfully minimized by the rigid restriction in salt intake.

TABLE 2

COMPLICATIONS OF THERAPY WITH CORTISONE AND ACTH
Fullness of face
Œdema
Congestive heart failure
Hypertension
Acne
Hirsutism
Alkalosis
Euphoria
Insomnia
Striæ
Delay in wound healing
Pigmentation (only with ACTH)
Convulsions
Depression
Psychosis
Diabetes mellitus
Osteoporosis
Transient adrenal insufficiency (only with cortisone)

Alkalosis, which sometimes occurs as a complication of treatment, is important because it is so often associated with hypopotassæmia as well as hypochloræmia. The reduction in the serum potassium level, however, may occur independently of the development of alkalosis. Such reduction in the serum potassium level constitutes a significant hazard to the patient, in that it is so often followed by various cardiac arrhythmias. The hypokalæmia may be prevented or treated by the daily oral administration of 2 to 6 grammes of potassium chloride or by the use of testosterone, which through its anabolic action tends to fix potassium in the cell.

The prolonged use of cortisone will occasionally induce *adrenal cortical insufficiency*. This is a transient phenomenon which usually disappears with-

in several days and rarely persists for longer than two to three weeks. The manifestations of adrenal insufficiency become evident only after therapy is discontinued, and are characterized mostly by the failure to develop an adequate eosinopenia, and an increase in the urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated compounds after the administration of a test dose of corticotrophin. Asthenia and anorexia are sometimes present, and only rarely does actual vascular collapse occur. It is a wise precaution not to discontinue cortisone after its prolonged use if an immediate surgical procedure is contemplated or if an acute infection develops.

TABLE 3

CONTRAINDICATIONS TO THE USE OF CORTISONE AND ACTH
Semiquiescent or active pulmonary tuberculosis
Gastric and duodenal ulcers
Previous psychotic states
Osteoporosis
Diabetes mellitus
Diverticulitis

None of the complications which follow the use of cortisone is permanent in character. With reduction in dosage or discontinuance of treatment they will disappear. Subsequent use of the steroid is not necessarily followed by a recurrence of the complications previously encountered.

In addition to the complications outlined above there are some *contraindications* to the use of cortisone (table 3). These contraindications are by no means absolute, but in these special circumstances the dangers associated with the use of the steroid must be weighed carefully against the benefits to be derived. Incompletely healed pulmonary tuberculosis may become disseminated after the use of cortisone, since fibrosis is interfered with or delayed. Perforation of peptic ulcers and of inflamed diverticula have been reported following the use of both corticotrophin and cortisone. Intensification of already existing osteoporosis may result in fractures, whilst diabetes mellitus may become worse and difficult to control. Pre-existing psychotic states may be intensified, ameliorated, or altered during treatment, and it is almost impossible to determine the character of the response before therapy is instituted. Finally, both ACTH and cortisone tend to mask symptoms and signs of progressive underlying disease. Since these hormones may reduce fever, abolish pain, and create a sense of comparative well-being without necessarily altering the pathologic process, acute medical or surgical emergencies may arise and progress with a minimum of objective signs.

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THE NATURE OF ACTH

A REVIEW OF THE PRESENT POSITION

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The term adrenocorticotrophic hormone—commonly abbreviated to ACTH—was originally coined to describe that substance present in extracts of the anterior lobe of the pituitary gland which possessed the ability, on administration to hypophysectomized animals, of preventing or curing the atrophy of the adrenal cortices which follows removal of the anterior pituitary gland in experimental animals. Until a few years ago it was generally believed that ACTH was of a protein nature and possessed a number of different activities. As a result of intense investigation during recent years, both the nature of ACTH and the physiological significance of it have been called in question and, although investigation has so far yielded no clear-cut final position, it seems desirable at the present time to review a field of interest which has so rapidly become confused and confusing. In order to provide the reader with some perspective from which to review the present position a brief historical introduction is included.

In 1914, Simmonds discovered the disease which was subsequently to bear his name. Unfortunately, and unnecessarily, the ponderous neologism 'panhypopituitarism' has been introduced in recent years to replace the simple eponym, although there seems to be little reason why the term 'Simmonds' disease' should not continue in use. Investigation by Simmonds in 1918, and others, demonstrated that the condition was associated with necrosis of the anterior lobe of the pituitary gland, and that atrophy of the adrenal glands as well as of other endocrine organs was usually observed. Already at this time experimental evidence was accumulating to suggest that the anterior pituitary gland influenced other endocrine organs, and in particular may be mentioned the investigations of P. E. Smith and of B. M. Allen in 1916, who found that extirpation of the hypophysis in amphibia resulted in atrophic changes in the thyroid gland and in the gonads. Smith's later investigations showed that it was the *pars glandularis* of the pituitary gland in amphibia which was of importance in influencing other endocrine organs, and he was also able to demonstrate that hypophysectomy induced atrophy of the cortical but not of the medullary component of the adrenal gland.

The extension of such observations to mammals was slow because of the difficulty of experimental removal of the pituitary gland, or of its various parts, in small mammals, but later Smith succeeded in hypophysectomizing the rat (1927, 1930) and showed that the profound atrophy of the endocrine glands which occurs after ablation of the pituitary gland in such a mammal

could be prevented or cured by the daily implantation of anterior pituitary tissue.

In 1933, Collip and his collaborators prepared extracts of the anterior pituitary glands of cattle which contained a substance capable of preventing or curing the atrophy of the adrenal glands which normally follows hypophysectomy in the rat, and which was able to bring about a marked hypertrophy of the adrenal glands on administration to normal animals. As the result of these investigations of Collip, and of others along similar lines, the substance active in maintaining the adrenal cortex in hypophysectomized animals was shown to be different from the anterior pituitary substances which stimulate somatic growth, thyroid enlargement or gonad activity in hypophysectomized rats, and so the idea of a separate 'adrenocorticotrophic hormone' was born. The same factor has at various times been called the adrenotrophic hormone, the interrenotrophic hormone, and corticotrophic hormone. In the present article the abbreviated form of 'adrenocorticotrophic hormone', namely 'ACTH', will be used.

As hypertrophy of the adrenal cortex can be brought about in normal animals as the result of numerous non-specific stimuli, such as the administration of toxic substances, it was essential, at least in the early stages of the investigation on the nature of ACTH, that all the experiments involving the detection and assay of this substance should be carried out in hypophysectomized animals, usually rats, in which the adrenal cortex is unaffected by non-specific stimuli. This naturally delayed the progress of purification of the active material, but in 1943 two laboratories independently and almost simultaneously announced the isolation from pituitary glands of a protein highly active in inducing repair of the adrenal glands in hypophysectomized rats, or in preventing atrophy of the adrenal glands if therapy were instituted immediately after hypophysectomy.

'PROTEIN-HORMONE' ACTH

In 1943, Li, Simpson and Evans prepared their protein from sheep pituitary glands and believed it to be pure and free from other anterior hypophyseal hormones, whilst in the same year Sayers, White and Long obtained a similar material from pig pituitary glands. The two preparations from different species of tissue exhibited similar physiological activities and similar chemical and physicochemical properties, including a molecular weight of 20,000. This material will subsequently be referred to as 'protein-hormone' ACTH.

In the following year Professor C. N. H. Long in collaboration with George Sayers and others observed that when protein-hormone ACTH is administered to a hypophysectomized rat the ascorbic acid and cholesterol contents of the adrenal glands are both rapidly reduced, and concomitantly there are signs of increased secretion of adrenocortical steroids. This led in 1948 to the development of a sensitive assay method for ACTH based on the rapid reduction of the adrenal ascorbic acid content in hypophysec-

tomized rats, brought about by a single injection of the ACTH under test. It will be convenient to refer to this method for the detection and assay of ACTH as the Sayers' test, and it may be pointed out at once that since 1948 much research has been carried out concerning the nature of ACTH in which the activity of the preparation has been determined entirely in terms of its ability to bring about reduction of the ascorbic acid content of the adrenal glands of the hypophysectomized rat.

Before 1948, ACTH was something of an academic curiosity. It had been employed occasionally in the treatment of Simmonds' disease and in other endocrine disturbances, but there was no obvious use for it on a large scale clinically, and very little material was in fact available, even for experimental work. In 1948, however, Hench and his colleagues at the Mayo Clinic found that both cortisone and ACTH could alleviate in a striking fashion the symptoms of rheumatoid arthritis, and ACTH at once became a substance of wide importance and interest. Furthermore, in the previous year Li had stated that when ACTH protein-hormone was subjected to hydrolysis by pepsin or by acid under controlled conditions, the hormonal activity was found in the hydrolysed fragments (the peptide residues) of the original protein molecule. From such partially hydrolysed preparations of the ACTH protein-hormone, Li obtained by various fractionation methods peptides which he believed to be pure ACTH (Li, 1950). The average peptide size of the material prepared by Li was found to be about eight amino-acid units, and the most active preparations were in some instances more than twenty times the activity of the original protein-hormone ACTH in the Sayers' test. The possibility that such peptides were pure and could be prepared by purely synthetic methods was an attractive one, and much investigation was directed towards the artificial production by chemical means of such possibly biologically active peptides, particularly with a view to their ultimate utilization in the treatment of clinical conditions such as rheumatoid arthritis. Whether or not the belief was justified that ACTH could be of outstanding value in clinical medicine will not be considered here, but whatever the outcome of the clinical investigations may be it is certain that the stimulus given to research on peptide chemistry by these investigations of Li has been of very great value in the field of endocrinology in general.

'SMALL MOLECULE' PREPARATIONS OF ACTH

The idea that ACTH was a protein of moderate molecular weight was not in agreement with many earlier observations. As long ago as 1933, Anselmino, Hoffmann and Herold had shown that ultrafiltrates of pituitary extracts prepared in slightly acid medium would bring about enlargement of the adrenal glands of mice. Since these tests were carried out on animals which were not hypophysectomized, they were not entirely convincing, but ten years later Tyslowitz showed by tests on hypophysectomized rats that ACTH activity could pass through cellophane membranes upon dialysis and

ultrafiltration, and similar methods have more recently been developed by C. J. O. R. Morris and his colleagues. It would not be expected that a protein of molecular weight 20,000 would pass through cellophane membranes of the type employed in these experiments. Furthermore, in 1950, Lesh, Hays and their colleagues, using fractions obtained from the protein hormone by pepsin digestion, were able, by a process of fractionation between water, phenol and ether, to obtain fractions 100 to 150 times as active as the protein hormone in the Sayers' test; they estimated the molecular weight of the active material to lie between 2,500 and 10,000. It is clearly impossible that such substance could be a fragment of a native protein hormone having a molecular weight of 20,000 and only 1 per cent. as active as this most highly active preparation.

Professor E. B. Astwood and his colleagues were the first to separate protein-hormone ACTH into highly active and relatively inactive fractions without a step obviously involving hydrolysis. They had observed in 1950 that ACTH activity in crude anterior pituitary extracts could be adsorbed from solution under appropriate conditions by cellulose, or better by oxidized cellulose (oxy-cellulose), and that subsequent elution yielded highly active material. When they passed a preparation of the protein hormone obtained from George Sayers through a column of cellulose they found that most of the protein passed rapidly through and emerged little changed in properties, except that its biological activity was greatly reduced. A small fraction which passed more slowly through the column, because of successive adsorptions and elutions, was found to be much more active in the Sayers' test (Astwood, Raben and Payne, 1952). These results suggested that the active material could be separated from the protein hormone without a step involving hydrolysis and that the protein hormone itself might not be of physiological significance.

Observations in keeping with this view were obtained by Dixon, Moore, Stack-Dunne and Young (1951). These investigators had concluded from preliminary experiments that the active material might well be basic in nature. The experiments of Astwood and his colleagues, involving the adsorption of the active material on oxy-cellulose (which contains COOH groups and is therefore acidic in nature), with its subsequent elution by a stronger acid, were in agreement with the view that the active material was basic in nature, forming a combination with the oxy-cellulose of the type of a salt, from which the active material could be released under the influence of a stronger acid. Dixon *et al.* (1951) used a synthetic carboxylic acid resin for the fractionation of ACTH, such a resin being in essence a synthetic insoluble organic acid containing a large number of COOH groups. When protein-hormone ACTH was passed through a column of a suitable ion-exchange carboxylic resin, 50 to 100 per cent. of the biological activity was recovered in fractions which passed through the column more slowly than the main part of the protein, and which contained probably less than 5 per cent. of the total peptide or protein material. The almost inactive protein

component which emerged first from the column was similar in general properties to the original protein-hormone ACTH, with the exception that its biological activity was reduced almost to negligible levels.

All these observations of a very different nature and from different laboratories were in agreement with the view that the active substance was not the protein hormone *per se* but that a smaller molecule, of much higher activity, carried on the protein hormone by adsorption or possibly by some type of salt linkage. The fact that the protein hormone was acidic in nature, whilst the small fragments which could be removed from it by oxy-cellulose or by ion-exchange resins appeared to be basic, would agree with the idea that the basic active material was carried in a type of salt linkage on the relatively acidic carrier protein molecule. Whether or not the protein hormone was itself of physiological significance was still not clear as the result of these investigations, but the possibility had to be considered, and must still remain for consideration, that the protein-hormone ACTH is in fact not a biological entity but is merely an example of a protein which withstands the somewhat drastic procedures that were originally used for the extraction of ACTH, and which thus survives to adsorb on to itself the small highly active molecule which is the true ACTH.

It perhaps should be emphasized once again at the present stage that the ACTH activity we have been considering with respect to the researches carried out since 1948 has largely been that observed in the Sayers' test, that is, activity in reducing the ascorbic acid content of the adrenal gland of the hypophysectomized rat. The properties of the most highly active preparations active in this respect, prepared by methods which involve no obvious hydrolytic step, are in agreement with the view that these materials are peptide in nature, although the evidence here is by no means complete. For instance, the biological activity can be destroyed by trypsin, pepsin, papain, carboxypeptidase and other enzymes, which would agree with the view that one or more peptide bonds are present and essential for the biological activity. Biological activity is also lost when treatment is applied, such as acetylation, which destroys the integrity of amino-groups, and this suggests that one or more amino-groups may be essential components of the active molecule. As has already been indicated above, active fractions behave in a basic manner, and it may well be that the active substance itself is basic in nature.

Since active preparations can retain activity after treatment by pepsin or by acid under controlled conditions, it appears that the biologically active material is not lost, at least in part, by the hydrolysis of some peptide bonds, and this is in agreement with the view that if the active material is a peptide the chain is unlikely to be a long one. However, the evidence that the active material is peptide in nature is far from complete.

THE QUESTION OF MULTIPLE ACTH'S

As the result of the work of Reichstein, Kendall and others from 1934

onwards it was realized that the adrenal cortex contains more than one steroid capable of keeping an adrenalectomized animal in good health, and ultimately it has been appreciated that there are at least seven such active steroids in extracts of the adrenal cortex, and possibly more. The investigations of Pincus and his school, and more recently of I. E. Bush, have indicated that two of these steroids, namely corticosterone and 17-hydroxy-corticosterone, furnish the major part of the secretion of the adrenal cortex, and Bush has shown that the relative proportions of these two steroids, which are different for different species, are not in most instances altered by the administration of ACTH, although the total amount of steroid secreted can be increased by the action of ACTH. On the basis of these findings it is therefore unnecessary to consider seriously the suggestions which have been made from time to time that there are possibly as many ACTH's as there are active steroids in the adrenal cortex. On the other hand, there is some evidence that the adrenal cortex is itself a complex organ and that different parts of it may have different functions and be under different types of control. Thus Greep and Deane in 1947 provided evidence that the *zona glomerulosa* of the adrenal cortex continues to function after hypophysectomy, and therefore can secrete steroid hormone independently of ACTH liberated by the pituitary gland. Selye believes that adrenal steroids may safely be divided into two classes: gluco-corticoids, which are primarily concerned in the control of carbohydrate metabolism, and mineralo-corticoids, which are primarily concerned with maintaining an adequate mineral balance in the body. He believes that the processes of control of the secretion of gluco-corticoids and the mineralo-corticoids from the adrenal cortex are not identical, and that which is normally called ACTH is a gluco-corticotrophic hormone (Selye, 1951), that is, one which stimulates the adrenal to produce gluco-corticoids. Selye further considers that growth hormone* possesses mineralo-corticotrophic effects, but concludes that the presence of ACTH is necessary in order that growth hormone may bring about its mineralo-corticotrophic effect and that growth hormone is unable to elicit its potential mineralo-corticotrophic action after the adrenal cortex has become atrophic, either owing to hypophysectomy or to excessive dosage with adrenal steroids. So far little evidence either in support or in contradiction of this aspect of Selye's work has accrued, and its general acceptance must await further investigation. Nevertheless, as will be seen below, there is good experimental evidence that growth hormone can exert some effect on the adrenal cortices of hypophysectomized animals.

EFFECT OF ACTH ON THE ADRENAL CORTEX

The fact that hyperplasia of the adrenal cortex can under some conditions bring about virilism in women has long been recognized and the isolation of androgens from the adrenal cortex by Reichstein, Kendall and others gave some support to the idea that androgens are among the secretory

*The somatotrophic hormone of Selye is the same as the growth hormone of others.

products of the adrenal glands. However, even now, convincing evidence that androgens are secreted by the adrenal cortex under normal conditions is not complete, although the recent investigations of Nelson and Samuels, among others, render such a view highly probable. Whether the secretion of androgens by the adrenal cortex is stimulated by the action of ACTH has still finally to be determined. It is true that after the administration of ACTH a rise in the urinary 17-ketosteroids can be observed, but such a rise might result from the excretion of degradation products of, for example, corticosterone and 17-hydroxycorticosterone, and does not conclusively demonstrate that under the influence of ACTH the adrenal cortex has itself secreted androgens.

It can be said that there is no convincing evidence at the present time that different pituitary factors are needed for the selective secretion of different adrenal steroids, and it may be concluded that what we now call ACTH is capable of stimulating the secretion of those steroids which are at present accepted as the major secretory products of the adrenal cortex.

Evidence of a different type from that considered above was brought to bear on the problem by Stack-Dunne and Young (1951), and by Dixon, Stack-Dunne, Young and Cater (1951). These authors compared the activities of pituitary extracts in the Sayers' test and in an 'adrenal repair' test based on the increase in the adrenal weight of the rat hypophysectomized one to three weeks previously, induced by pituitary treatment. They found a very big discrepancy in the relative adrenal-weight increasing and ascorbic-acid-reducing activities of different pituitary preparations, observing that preparations of pituitary growth hormone were particularly effective in stimulating adrenal repair in the hypophysectomized rat, although almost devoid of activity in the Sayers' test. Partial separation of the two factors was obtained by fractionation on an ion-exchange resin. Cater and Stack-Dunne (1952) have also demonstrated that pituitary fractions which are particularly active in increasing the adrenal weight in hypophysectomized animals also stimulate mitotic activity in the adrenal cortex, whereas ascorbic-acid reducing fractions show only very feeble activity in this respect. These investigators make no definite conclusions as to the physiological significance of their observations, although they point out that their findings would agree with the view that the adrenal-weight increasing preparations, which might or might not be identical with growth hormone, are active in bringing about a deposition of cholesterol in the adrenal cortex, whilst the ascorbic-acid reducing preparations are active in assisting the ultimate conversion of the cholesterol to secreted adrenal steroids.

In their experiments Dixon, Stack-Dunne, Young and their collaborators (1951) observed that procedures liable to lead to hydrolysis of peptide material caused a proportionately greater loss in the adrenal-weight increasing activity of their pituitary fractions than in the ascorbic-acid reducing activity, and similar observations have recently been recorded by Li. The simplest interpretation of these findings is that the adrenal-weight

increasing factor is more easily inactivated by hydrolysis than is the ascorbic-acid reducing factor. Some clinicians (e.g. Prunty, 1951) have found serious discrepancies between the clinical effectiveness of preparations of ACTH and their activity determined (as it now often is) in terms of the Sayers' test. Whether such preparations contain varying amounts of adrenal-weight increasing factor and this factor contributes to the clinical effectiveness of the preparations remains to be determined.

GENERAL CONCLUSIONS

We may define ACTH as that anterior pituitary substance which, under appropriate conditions, brings about a fall in the ascorbic acid content of the adrenal glands of the hypophysectomized rat. Defined thus we can say that the so-called protein-hormone ACTH isolated in 1943 is not the pure hormone, but probably consists largely of inactive protein carrying a small amount of highly active substance, the latter being at least 100 to 150 times as active weight for weight as the complex of protein plus active substance. The nature of the active substance has as yet not been determined, but the balance of evidence agrees with the view that it is a peptide of relatively small molecular weight.

In addition to ACTH, defined as above, at least one other pituitary factor exerts an influence on the adrenal cortex of the hypophysectomized rat, and preparations of growth hormone are usually rich in a factor which increases the weight of the adrenal glands of the hypophysectomized rat. There is no evidence as to whether or not growth hormone is identical with the adrenal-weight increasing substance, but it is probable that the latter is not identical with what we now call ACTH.

The view may tentatively be considered that the pituitary factor which increases the weight of the adrenal cortex is particularly concerned with facilitating the deposition of cholesterol in the adrenal cortex, whilst ACTH as defined above is especially concerned in facilitating the conversion of the cholesterol in the adrenal cortex to the secreted adrenal steroids.

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THE TREATMENT OF THYROTOXICOSIS

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THE rational treatment of thyrotoxicosis has not yet been achieved. It must wait on the elucidation of the causes of the disease, and in particular on the partition of blame between the various organs incriminated: the higher centres of the brain, the hypothalamus, the anterior lobe of the pituitary gland, the adrenal cortices and the thyroid gland itself. Discussion of treatment nowadays is concerned almost entirely with different methods of eliminating hyperthyroidism, a process which, in a large proportion of cases, cannot be regarded as affording more than symptomatic relief. Although it seems probable, both on theoretical grounds and from the results of treatment, that disorder of the thyroid gland is itself in some instances the cause of thyrotoxicosis, and that the removal of the gland in these cases results in cure, it is certainly true that in many more the thyroid is the victim of a disease elsewhere and that its elimination removes the more important effects of the disorder, leaving its cause still untouched.

It is too soon as yet to be satisfied with results. It is easy to be hypnotized by the sight of hundreds of thyrotoxic patients passing rapidly through an efficient therapeutic machine to the goal of normal thyroid function. Whether we are addicts to partial thyroidectomy, or to one of the now numerous antithyroid drugs, or to radioactive iodine, we may be so dazzled by our results, so much better than those of our predecessors, that we may be blinded to our few partial failures, dismissing them as due to the constitutional inferiority or neurotic imbalance of our patients. The treatment of hyperthyroidism has now reached so high a level of routine efficiency that there is time and mental energy to spare for consideration of the rare deaths (about 0.1 per cent. in the larger clinics), the rarer occurrence of permanent tetany or recurrent laryngeal palsy, and the relatively common residual symptoms of autonomic and psychological imbalance. In particular, there is time now to think about the immediate postoperative condition of the patient. No longer frightened by the now remote possibilities of death from shock or hæmorrhage or crisis, we can usefully ponder upon the fact that some patients can eat a hearty meal on the evening of operation and demand to be discharged on the following day, whereas others pass through a day or two of presumably avoidable discomfort.

Many of these heart-searchings are of solely surgical importance. From the point of view of the general practitioner and the physician there are several questions to be answered:—

WHAT CAN BE DONE APART FROM ELIMINATION OF THYROTOXICOSIS?

Can anything be done for the patient apart from the elimination of thyro-

toxicosis; something more fundamental, concerned more closely with the cause of the disorder? It is unfortunate that concentration on modern and ever more efficient methods of detoxication have deflected the attention of many from ancient maxims which have not lost their force. The apparent origin of an individual attack of thyrotoxicosis is often to be found in physical or psychological stress. The cure of thyrotoxicosis does not by itself effect the cure of the patient, and he may be expected still to respond abnormally to stresses which leave the healthy man or woman physically unimpaired. His further treatment must often be psychological in aim, but it must be admitted that psychiatry appears to have achieved little. The commonsense handling of the situation by the practitioner is usually more effective than the specialized approach. We must ask why the patient became thyrotoxic. Given a thyroid unduly susceptible, for genetic or for unknown reasons, to the winds of chance, whence blew these winds? Can the patient be kept out of the draught in future? The thyroid once having gone wrong is likely, if the patient retains it, to go wrong again. The patient's history may give clues to the earlier straws which weakened the camel's back. Such straws may be avoidable, or unavoidable and a continuing risk. The immediate predisposing causes, the last straws which broke the camel's back, are often obvious. Among them are puberty, childbirth, the menopause, severe infections, psychological strains, and the unwise administration of thyroid in the treatment of obesity. Often the patient can be protected against the last straw or from the wind which blows it his way, but unfortunately the immediate causes of thyrotoxicosis are interchangeable, and in avoiding one the patient may encounter another. There is no disorder in which it is more important to study the patient as a whole, and in particular his family history, environment, family life, general health (especially liability to infections), and dietetic habits. These last are important, not only because of the increased need of vitamins by the thyrotoxic patient, but because there is some evidence that vitamin A at least may have an antithyroid effect. Moreover, the caloric needs of the thyrotoxic patient may be enormous and may amount to as much as 6000 or 7000 calories a day. A negative calcium balance is the rule and extra calcium in the diet may be advisable. The liver often bears the brunt of the disease and demands a high intake of proteins.

IS IT JUSTIFIABLE TO RELY ON ANTITHYROID DRUGS?

This is a controversial question and one which will not be answered finally until the end of the century, by which time it will have been possible to follow through their lives a sufficiently large number of patients treated with thiouracil derivatives and their precursors and successors. By that time such a 'follow-up' may not be worth while. It would appear at present that antithyroid drugs almost invariably cause a remission of the existing attack of thyrotoxicosis. They probably have no permanent effect upon the thyroid. Therefore in those patients in whom the disease would be per-

manent if left untreated (including all those suffering from toxic nodular goitre) relapse after the cessation of treatment is certain. But all patients do not belong to this class. Some of us are old enough to remember the days when thyroidectomy was a hazardous operation, hardly considered unless the disease was severe enough to endanger the life of the patient, or at any rate his capacity to live an independent life. Patients less severely affected were put to bed for prolonged periods and treated with sedatives, while efforts were made to eliminate the stresses which had caused the breakdown. Some of them recovered completely, though whether many recovered permanently is doubtful. Their thyroid glands and their abnormal reactions to stress remained. So now, some patients, who in my own experience are always young girls with thyroids diffusely and only slightly enlarged and a mild degree of thyrotoxicosis, make apparently complete recoveries after treatment with antithyroid drugs. But their thyroids and their abnormal reactions are unchanged. They may never again encounter the identical last straw which formerly broke the camel's back, but any last straw will do, and the patient remains at risk, for ever watching the wind to see which way the last straws are blowing.

This is not to say that an attempt at the medical treatment of such patients is unjustifiable. The girl's life may change and with it her reaction to stress. The repeated endocrine readjustments of a woman's life may give her ultimately a balanced endocrine system, capable of withstanding stresses which would formerly have caused a thyroid breakdown. No harm is done by giving her the chance to make these adjustments, but thyroidectomy should be recommended when the first relapse occurs. It is unfair, especially to a patient suffering from a disorder in which anxiety is so prominent a symptom, to play cat and mouse with the disease.

In some circumstances this advice may need modification. The skill of many excellent general surgeons falls below the standard needed in thyroidectomy. It is an operation in which a small but important proportion of cases presents great difficulties even to the expert. Although in special clinics the death rate is of the order of 0.1 per cent., in many hospitals it is far higher. A life-time of treatment with thiouracil may be the lesser of two evils.

WHAT ARE THE DRUGS AVAILABLE FOR MEDICAL TREATMENT?

Let it first be said that iodine is not one of them. It plays an excellent, indeed a necessary, part in the preparation of the patient for operation, but none in the purely medical treatment of thyrotoxicosis. It damps down the disease for a while, induces in both patient and doctor a sense of false security, and has been compared by McEwen to morphine in the 'acute abdomen'.

The first true antithyroid drug was *thiourea*, which has since been superceded by *thiouracil* and later by methyl and propyl thiouracil. There is

nothing to choose between these two derivatives of thiouracil, except that the methyl derivative is easier to make. Aminothiazole has been tried and abandoned because of its toxicity. Thiobarbital and ethyl thiouracil are also more toxic than methyl and propyl thiouracil and have no advantages over them. *Methimazole* (methylmercaptoimidazole) is still under trial. Preliminary communications suggest that it is both more effective and less toxic than methyl thiouracil, but more prolonged trial in special clinics will be necessary before its general use can be recommended. In general practice, for the time being, the use of ***methyl thiouracil*** only is recommended, for it is of this compound that the largest amount of knowledge has accumulated.

The usual dose is 200 mg. twice daily. It is given until the signs and symptoms of the disease are completely under control. Rest in bed is usually no longer necessary and some patients may even be allowed to continue their work, but each case must be considered individually and much care and judgment used in deciding how much rest and sedation should be enjoined and to what extent it is advisable to separate the patient from her environment. The old principles of treatment have not ceased to be applicable.

When the disease has been completely controlled the dose is gradually reduced. Control may take from one to three months. The rate of reduction depends upon the individual, but for the average patient the dose can be halved every month after control has been achieved, until a dose of 50 mg. daily is reached. It is kept at this level until the patient has been a year under treatment, when it is discontinued. Interference with the usual course may occur in several ways:—

(a) The patient may be intolerant of thiouracil. Intolerance may take many forms. Rashes of various kinds, swelling of the joints, nausea, drug fever, and enlargement of lymphatic glands are rarely severe enough to warrant a change of treatment. Rashes usually respond to promethazine hydrochloride and other antihistaminic drugs. On the other hand, the occurrence of agranulocytosis is a bar to further treatment with thiouracil derivatives. It occurs in about 1 per cent. of cases, usually, but not invariably, early in the treatment. Patients should be warned to report immediately if they have a sore throat. If when they report they are found to have a total white cell count of under 3000, or a polymorphonuclear percentage of less than 25 per cent. even of a normal total, they should at once be admitted to hospital, where, if their condition deteriorates, they should be treated with blood transfusions and massive doses of penicillin. It has recently been reported that corticotrophin is effective, but in view of the tendency of agranulocytosis to ameliorate spontaneously the claim cannot yet be accepted.

(b) The patient may develop myxœdema or further enlargement of the thyroid. Both are the results of overdosage. They do not occur if the patient is seen weekly and carefully observed. Should either occur, the treatment should be stopped and restarted with a smaller dose when the hypothy-

roidism has cleared up or the goitre returned to its former size. Rarely, increased exophthalmos may occur. This is an indication for abandonment of the treatment, or at least for extreme caution.

(c) Relapse may occur when the dosage is reduced. Treatment for the prescribed year must then be continued with a dose high enough to prevent it. In such cases it may be difficult to find a dose which will control the thyrotoxicosis without producing further thyroid enlargement.

WHAT ARE THE CONTRAINDICATIONS TO THIOURACIL TREATMENT?

There are no absolute contraindications, but it is obvious that in the presence of a retrosternal goitre or severe pressure symptoms, thiouracil should be used with extreme caution, lest a slight enlargement of the gland should occur. In the opinion of the team in the New End Thyroid Clinic, nodularity is also a contraindication. We have not yet known a prolonged remission of thyrotoxicosis to occur in the presence of nodules. The intelligence of the patient and his willingness to cooperate fully and report regularly must be considered seriously, and the slightest deviation from the rules laid down for his safety is an indication for thyroidectomy. But perhaps the most serious contraindication to medical treatment in some individuals is that it imposes on a patient, already perhaps unduly nervous, a period of prolonged reliance on his doctor which cannot fail to exaggerate any hypochondriacal traits which may already be present.

Some doubt still exists as to whether or not pregnancy should be regarded as a contraindication to the use of thiouracil. The subject is of some importance because of the frequency with which thyrotoxicosis occurs in pregnant women. McGavack has collected reports of 34 women treated throughout pregnancy. Of these, 30 produced normal babies, and 3, babies with goitres; the condition of one was unrecorded. The babies with goitres ultimately suffered no harm, but 10 per cent. of abnormal babies is a proportion which engenders doubt, and it would seem best to avoid thiouracil when possible. Thyroidectomy, after preparation with Lugol's solution, should be undertaken as early as possible in the pregnancy. It carries no risk of miscarriage. In severe thyrotoxicosis, when preparation with thiouracil seems necessary, no attempt should be made to reduce the metabolism to normal. The basal metabolic rate of the healthy woman is raised in pregnancy, and that of the thyrotoxic woman should be lowered only sufficiently to convert a severe into a moderate degree of thyrotoxicosis. Thereafter, iodine should be given and thyroidectomy performed. If for cogent reasons thiouracil is continued to term, the mother should not feed her child at the breast, for the drug appears in high concentration in the milk and may induce goitre and hypothyroidism in the suckling.

Severe exophthalmos also causes doubt It may be increased by any treatment which diminishes hyperthyroidism. Faced with an exophthalmic

patient whose thyrotoxicosis demands treatment, the physician is on the horns of a dilemma. Probably no single physician has sufficient experience to make an *ex cathedra* pronouncement. My impression, most tentatively expressed, is that thiouracil, which acts less suddenly, is less dangerous than surgery, and it may be that the danger to the eyes is reduced if thyroid is given concurrently.

WHAT ARE THE INDICATIONS FOR SURGERY?

Many of these are implicit in what has already been said. The large goitre demands surgical treatment because of pressure symptoms or for æsthetic reasons. The nodular goitre demands it because thiouracil in such cases never produces a prolonged remission, and because, especially when there is only one nodule, there is a small but important risk of malignant change. Indeed, in all special clinics opinion has swayed back towards surgery as the best treatment for the majority of patients. The economic position of the patient is better protected by a method which, in most cases, rids him within two months of the necessity for further treatment. The cosmetic results, except for the inevitable risk of a keloid scar, are better, for within a month or two the scar is almost, or even quite, invisible at ordinary conversational distances.

But the question is wrongly posed, for nowadays there is no indication for surgery alone in thyrotoxicosis. The choice is between medical treatment and a combination of medical and surgical treatment. The patient, except in cases of the most extreme severity and in those complicated by congestive heart failure, is prepared as an out-patient. Admission to hospital is usually unnecessary until a day or two before operation. If the thyrotoxicosis is mild, iodine is given for the previous ten to fourteen days, usually as Lugol's solution, in dosage of five minims (0.3 ml.) three times a day. In moderate or severe cases, thiouracil is used as though for purely medical treatment until the signs and symptoms are controlled. Thiouracil has the disadvantage of rendering the operation of thyroidectomy more difficult in the occasional case. This disadvantage—a small one in comparison with the added safety which accompanies it—can usually be overcome by the administration of iodine for two to three weeks before operation. Some physicians prefer to combine the iodine in the preoperative period with methyl thiouracil; some (as at New End) forego the thiouracil for the final period and use iodine alone; others overlap the two drugs for various periods, giving at first methyl thiouracil alone, then a combination of methyl thiouracil with iodine, and, finally, iodine alone. Others administer thyroid as well. So far it seems that no advantage is attached to any one of these methods. All are excellent in their results, and it will be many years before any valid comparison can be made between them. Whichever method is adopted, the patient is usually out of bed in four or five days and out of hospital in from nine to twelve days.

ARE THERE ANY CONTRAINDICATIONS TO THYROIDECTOMY?

There are surprisingly few. Certainly auricular fibrillation is not one of them. Congestive heart failure demands careful treatment before operation, not only with thiouracil, but with the usual cardiological methods of rest, digitalis and diuretics.

WHAT IS THE OUTLOOK FOR THE USE OF RADIOACTIVE IODINE?

Although ten years have passed since the introduction of radioactive iodine, it is still too early to evaluate its place in the treatment (as opposed to the diagnosis) of thyrotoxicosis. It is known that I^{131}, like ordinary iodine, is concentrated for the most part in the thyroid gland, that the thyroid uptake is increased in thyrotoxicosis, and that the β-radiation produced within the cells of the thyroid is effective in reducing or even eliminating their activity. Two things have handicapped what might otherwise have been an enthusiastic reception of so untroublesome a treatment. In the first place, there is the fear of letting loose in the body so powerful and mysterious an agent. There is the fear of cancer, especially of the urinary tract, by way of which the drug is eliminated, and also of possible mutational changes in the germ plasm. Neither tragedy is at all likely to occur, and neither has yet been reported. In the second place, there is the difficulty of choosing the right dose for the individual patient, the amount, that is, which will cure the thyrotoxicosis without causing myxœdema. Several formulæ have been produced, but all depend in part upon an estimate of the weight of the gland, and such guesses are very rough ones. The obvious way out of the difficulty, that of giving a succession of fractions of the estimated total requirement, is not a good one, for too much time is required to plot first the reduction of thyroid activity, then the temporary exacerbation which follows, and finally, the subsequent steady state, which may not be achieved for two or three months; and this time must elapse before the next fraction is administered.

The fear of cancer or of changes in the germ plasm have caused most clinics to confine the treatment of thyrotoxicosis by I^{131} to patients who have passed the reproductive age and whose expectation of life is anyhow relatively short; and those in whom other forms of treatment are regarded as likely to be more than usually difficult or hazardous. Nevertheless, the opinion is gaining ground that before many years have passed I^{131} will become the method of choice in a far wider range of patients.

It must, however, be remembered that the use of I^{131} is essentially merely another method of thyroidectomy, less crude than surgery and with certain advantages and disadvantages when compared with the chemical methods now commonly in use. It may well be that before its use becomes general, there may be evolved a more rational treatment of thyrotoxicosis than one which aims merely at the elimination of an organ which is more often the main objective of the enemy's attack than the enemy himself.

THE ŒSTROGENS: SYNTHETIC AND NATURAL

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It is nearly thirty years since Allen and Doisy (1923) proved that a substance was produced by the ovary which had the power of causing growth changes in the tissues of the genital tract of the castrated rodent. As they were similar to those occurring at œstrus, substances capable of producing them have been termed œstrogens. Since their discovery, research on their mode of action has been continuous and clinical assessment has been made of their value in treatment. The former has not yet revealed the ultimate nature of their effects on tissues; the latter has led from the preliminary enthusiasm of empiricism to a critical appraisal of their uses in treatment.

A detailed discussion of their structure and biochemistry is not necessary, as this has already been considered fully in *The Practitioner* by Dodds (1949). It is only relevant to stress the steroid structure of those œstrogens occurring naturally in the body in contrast to the entirely different composition of others made synthetically (fig. 1a, 1b). Naturally occurring œstrogens are: œstradiol, œstrone and œstriol, of which the first is the one generally employed in practice. They are produced in the ovary, in the placenta during pregnancy, and also by the adrenal cortex. Although present in greater quantity in the follicular phase of the menstrual cycle, they are produced by the cells of the corpus luteum, and probably by the interstitial cells as well as by those of the follicle. The liver is largely concerned in their inactivation, and clinically the association of gynæcomastia with impaired liver function is well recognized. Since Dodds and his colleagues (1938) introduced stilbœstrol and opened up the field for deriving œstrogenic substances synthetically, many have been tried. The ones usually employed are, chemically, stilbenes (fig. 1b).

To the clinician the minutiæ of chemical structure are confusing, but they do remind him on the one hand of the similarity of the ovarian hormones to some others, and on the other hand, they give some reason to the ever increasing numbers of artificial œstrogens the powers of which he has to try to assimilate.

ACTIONS OF THE ŒSTROGENS

Œstrogens, like any other hormones, have specific actions on the end-organs responsive to them: metabolic and other general effects; and interactions with other ductless glands (fig. 2).

Actions on the end-organs.—All tissues derived embryologically from the Müllerian tract respond to œstrogens. The response is one of marked growth accompanied by cellular activity and concomitant metabolic changes. These

are seen particularly at puberty with the development of the genital system, during the menstrual cycle, and during pregnancy. Reynolds (1950) points out that they are concerned broadly with the physiological functions of growth, motility, and vascularity of the uterus, so that the biological

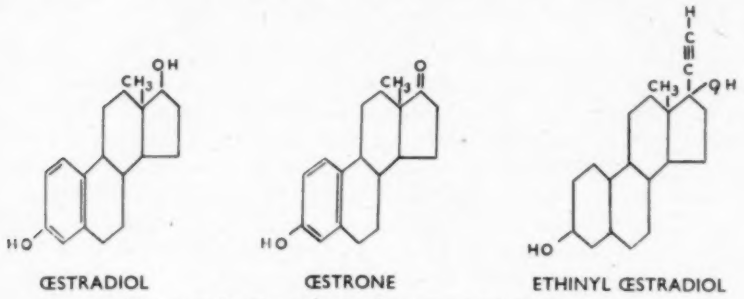

FIG. 1a.—Structure of natural œstrogens and a derivative.

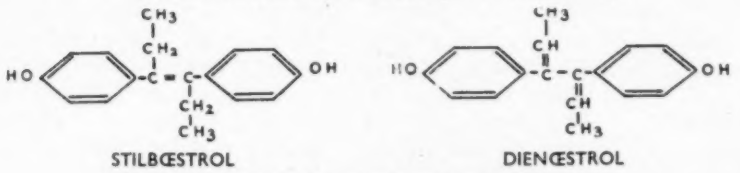

FIG. 1b.—Structure of commonly used synthetic œstrogens.

functions of nidation, pregnancy and parturition may be carried out. The ultimate mode of action of the hormone is still in doubt, but factors which may be of importance are that œstrogens have a stimulant action on the cell nuclei; that tissue respiration is affected; and that changes take place at the intercellular surfaces. Œstrogenic activity is also coincident with increased vascularity of the tissues.

The multiplicity of changes taking place in the endometrium and uterus during the menstrual cycle under the hormonic influence of œstrogens in the pre-ovulation phase, and of both œstrogens and progesterone in the post-ovulation period, far exceed the glandular and stromal alterations depicted in the simple customary diagrams. Besides the building up of the endometrium, this newly grown tissue has to be supplied with increased blood flow provided by the growth of the spiral subendometrial vessels; biochemical changes take place, and uterine motility is affected. All these activities are initiated by the œstrogens and completed by them with the consecutive action of progesterone. In its preparation to receive the fertilized ovum the endometrium has to metabolize and store glycogen which can be used as a source of nutrition for the ovum and for the growth and hypertrophy of the uterine muscle. The glycogen is transformed from glucose by enzymic action. Alkaline phosphatase is concerned in this activity and is

found in the uterine glands in the pre-ovulatory phase preceding the appearance of glycogen, which begins to appear in the basal part of the gland cells during the second week. If it is not mobilized later by progesterone the ovum may have difficulty in embedding. This may be a cause of infertility (Hughes, 1945).

Uterine motility, which is present particularly in the pre-ovulation phase of the menstrual cycle and during pregnancy, has been shown to be due to a muscle protein, actomyosin, the production and situation of which in the uterus is associated with œstrogen activity. Nor is the action of œstrogens on the uterus limited to the corporeal part only; the mucus secretion of the cervix also alters during the menstrual cycle. In the postmenstrual phase it is tough, cellular, and traversed by spermatozoa with difficulty. By the time

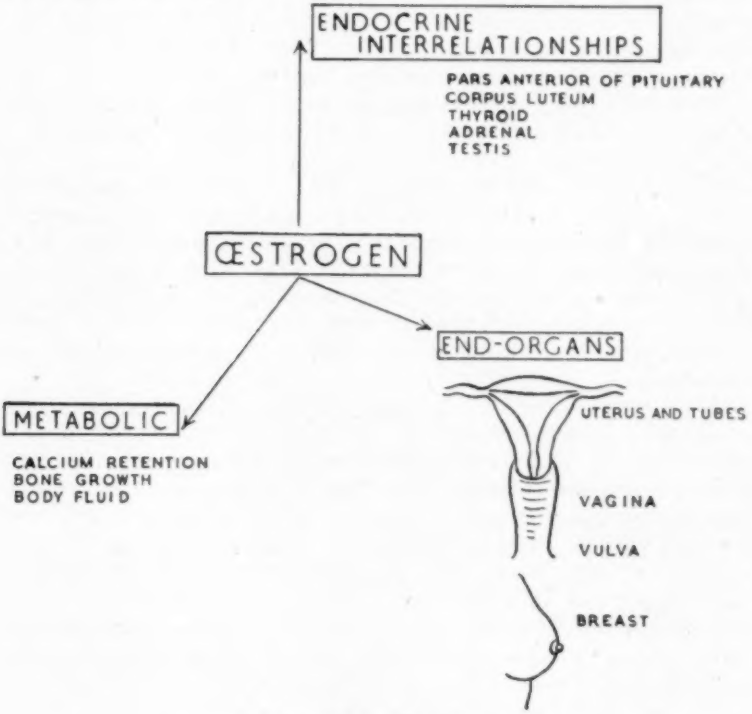

FIG. 2.—Actions of œstrogens.

of ovulation it has become more abundant, less viscous, and more easily permeable to the spermatozoa.

The vaginal epithelium is considerably modified by the œstrogens at puberty, during pregnancy, and in the menstrual cycle. The pre-puberty

condition of a thin membrane is altered to that of a multiple-layered, stratified epithelium. Coincident with this change is the appearance of Döderlein's bacilli and a strongly acid reaction of the vaginal transudate. During the menstrual cycle, vaginal smears show rhythmic alterations in the cells, which immediately after the period are mainly large round cells with a basophil reaction and accompanied by many leucocytes. Under the influence of œstrogen, cornified epithelial cells appear and increase in number. These are acidophil in reaction. The introital area of the skin round the vagina and that forming the labia are also responsive to œstrogens.

The secondary sex structures are responsive to œstrogen stimulation. The breasts develop at puberty and also undergo changes during the menstrual cycle. Œstrogens are probably responsible for proliferation of the gland tissue; but here again, as in the endometrium, the actions of œstrogens and progesterone cannot be artificially separated as they act synergically, and progesterone, too, produces growth of the breast. Skin pigmentation and hair development are related to œstrogen action.

Action during pregnancy.—During pregnancy there is a considerable increase in the quantity of œstrogens in circulation. This increase starts after the first three months with the formation of the placenta. Œstriol is the œstrogen mainly found. The œstrogens are responsible for many of the changes occurring in pregnancy and ensure uterine growth, hyperplasia of the muscle, the softening of the pelvic tissues and relaxation of the joints, and the further development of the breasts. The vaginal epithelium here shows mainly basophil cells, and a large number of characteristic cells are formed from its intermediate layer. These are boat-shaped, and hence are termed navicular cells, and from their presence in quantity pregnancy can be diagnosed.

The œstrogen production in pregnancy has been discussed in recent years in relation to two clinical problems. One has been the onset of labour. It was thought a few years ago that the onset of labour was associated near term with the fall in excretion of 'combined' œstrogen (i.e. œstrogens combined as glucuronidates or sulphates) and the appearance of 'free' or non-combined œstrogen. This has now been shown not to be the case (Clayton and Marrian, 1950; Swyer, 1952), so that giving œstrogens in an attempt to induce labour does not appear logical.

During the last decade the Smiths (1948) in numerous papers have put forward views that toxæmia of pregnancy, diabetes complicating pregnancy, and some cases of abortion may show alterations in the proportions of the endocrines, which they attribute to placental degeneration. In turn, the degenerating placenta may release a toxic substance which is the etiological agent of toxæmia. They believe that there is a deficient œstrogen and progesterone output associated with excess chorionic gonadotrophins, and have attempted to influence this by a high dosage of stilbœstrol sustained over many weeks. As confirmation of this work is still needed and the bio-

chemical aspects are extremely complicated there does not yet seem reason to employ œstrogens for this purpose.

Metabolic effects.—Œstrogens have an influence on calcium metabolism, causing its retention, and Albright (1947), and Reifenstein and Albright (1946, 1947) showed that clinically they could be used to increase calcium retention in the osteoporosis of the aged and in the healing of fractures, or in the postoperative phase of orthopædic work.

The influence of the œstrogens on water retention of tissues is well recognized clinically in the states of premenstrual œdema, weight gain, and tension. These actions appear to be due partly to salt retention and partly to altered capillary permeability.

Endocrine interrelationships.—The ovary and anterior pituitary interact by mutual stimulation and inhibition. Thus, in the early part of the menstrual cycle the ovary is stimulated by the follicular stimulating hormone (F.S.H.) to produce œstrogens which in turn inhibit the further production of F.S.H., and also help to stimulate the luteinizing process of the latter part of the cycle. Ovulation can be inhibited by high doses of œstrogens, and inhibition of the anterior pituitary activity at the menopause can similarly be effected. In the male, œstrogens are given for the same purpose in carcinoma of the prostate. Here the inhibitory action on the anterior pituitary results in a decrease in the secretion of testosterone by the testis.

The relationships between the adrenal cortex and the ovarian hormones are as yet more obscure, but the adreno-genital syndrome is an example. The frequent coincidence of a spell of amenorrhœa following some trauma or infection may be due to increased adrenal activity (stress reaction) and its effect on the ovary.

Carcinogenesis and the œstrogens.—Since the demonstration of œstrogenic activity on the endometrium and breast tissues the possibility of a relationship between œstrogen hyperplasia of the endometrium and carcinoma of the uterine body has been discussed. Several authors have analysed the frequency of hyperplasia in cases of adenocarcinoma, the relationship between a late and prolonged menopause to subsequent cancer, and the high proportion of this found in patients suffering from œstrogen-producing tumours of the ovary. It would seem that hyperplasia is not of itself a pre-malignant condition but that perhaps carcinoma arises more often following it, due to other as yet not defined causes. Thus œstrogens should not be used for a prolonged time if the tissues are unduly sensitive to them.

TREATMENT WITH ŒSTROGENS

The scope and uses of the ovarian hormones in treatment are by now much better defined and their indiscriminate use is not justified. It has perhaps been a pity that they have been made so easily available, and particularly that many women regard them as almost a necessity at the climacteric. The association of sex gland function with emotion brings many patients, who

may not in fact need glandular therapy, to the doctor. There is now other evidence than clinical impression of the importance of emotional factors in menstrual disturbances, and Theobald's (1936) observations in regard to the hypothalamus have been reinforced by the experimental work of Harris (1949, 1950).

Theoretically, œstrogens can be used on the principles of their actions as already mentioned. It is easier, however, to discuss their use in relation to conditions from a clinical aspect.

First, *disadvantages* of their use must be mentioned. Like any other endocrine substances they are employed mainly as substitutional therapy. Thus the patient with primary amenorrhœa cannot be made to menstruate regularly by their use. But substitutional treatment may provide an impetus effectively in some patients with secondary amenorrhœa. Secondly, if œstrogens are used for a prolonged time in sufficient degree (e.g. stilbœstrol, 3 mg. daily) they can cause suppression of the activity of the anterior pituitary. Thirdly, if used without due care and a proper plan, irregular uterine bleeding may result. In a neurotic patient this may prove as, or more, disturbing than the original symptoms; or in the older patient post-menopausal bleeding may start, thus raising the possible diagnosis of carcinoma of the uterus. It is clinically surprising how variable is the sensitivity of the uterus to œstrogens, even in old age. These remarks are not intended to detract from the use of ovarian hormones under suitable conditions, but to draw attention to possible disadvantages.

Mode of administration: dosage.—The substances used nowadays are mainly synthetic. Stilbœstrol remains a standard and is least expensive. Dienœstrol and hexœstrol are also used, though less powerful. These substances are practically always given orally (dosage range of stilbœstrol, from 0.1 mg. to 5 mg., according to the condition treated). Of the 'natural' œstrogens, œstradiol and ethinyl œstradiol are usually employed. The former is useful if injections are indicated (dosage, 10,000 i.u. [1.0 mg.] to 50,000 i.u. [5 mg.]). Ethinyl œstradiol is a very powerful substance given orally (dosage range, 0.01 mg. to 2 to 3 mg., the latter in cases of carcinoma only). Naturally derived œstrogens rarely give rise to 'toxic' symptoms of nausea and vomiting. Œstradiol may also be given as an elixir. Implantations of œstrogen intramuscularly are not necessary in the treatment of gynæcological symptoms, but may be useful in selected cases of carcinoma.

Application locally by ointment or intravaginal applicators is used in atrophic or inflammatory conditions of the vagina and vulva. The usual dosage here is œstrone, 0.5 mg. to the gramme of the ointment, or 0.1 mg. œstrone in bougie form.

The advisability or not of treatment.—Before embarking on a course of treatment with œstrogens the indication for their use should be clear. Menstrual symptoms may be produced by three main groups of causes (fig. 3). In this respect of diagnosis, stress may be laid particularly on the

part played by psychological factors such as fear and worry in the production of amenorrhœa, and the difficulty on occasions of proving the existence of a small submucous intracavitary fibroid which may cause troublesome and perplexing menorrhagia. Confession will prove a more effective treatment than the use of œstrogens in the former example; in the latter, the removal of the fibroid will cure the menorrhagia. Similarly, any irregular bleeding in an adult woman should indicate the need for very careful examination of

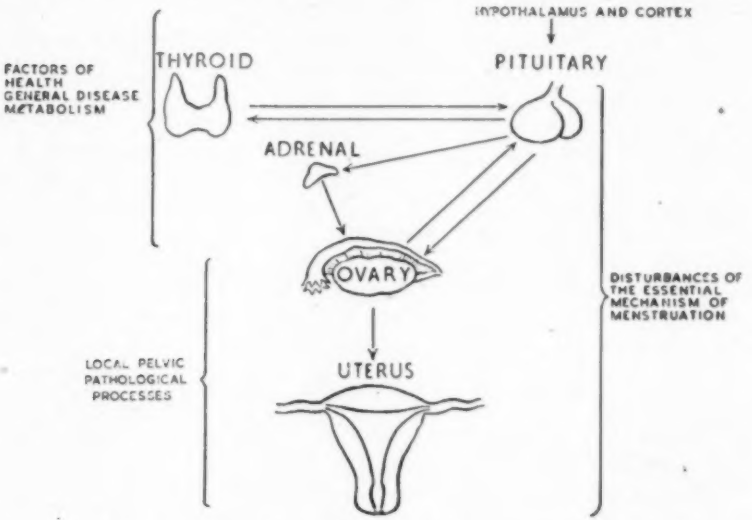

FIG. 3.—Main factors in the production of menstrual disorders.

the cervix. Finally, certain menstrual symptoms are often self-limiting conditions. Simple secondary amenorrhœa often rights itself, and dysmenorrhœa tends to lessen with the increasing maturity of the patient.

THE TREATMENT OF MENSTRUAL DISORDERS

Amenorrhœa.—When assessing the patient suffering from amenorrhœa the site of the functional failure has to be determined. This may be at the level of the anterior part of the pituitary gland, the ovary, or the uterus. On occasion, particularly if the amenorrhœa is of a primary type, if there is genuine doubt as to the late onset of the periods, or if the amenorrhœa is recurrent or associated with other symptoms and signs of endocrine dysfunction, the patient may need very careful examination and perhaps the aid of endocrine assays. The practitioner may well try endocrine treatment if the amenorrhœa is secondary in type, if it has persisted for some months, and if there is no underlying serious condition of which it is merely a

symptom. The best indication is if the irregularity is associated with difficulty in conception. Œstrogen treatment in cases of primary amenorrhœa is to all intents and purposes worthless.

When treating the amenorrhœic patient with œstrogens it is important to have a plan (fig. 4) which is understood by the patient or her nurse, otherwise confusion easily arises. The œstrogen is given rhythmically, and preferably accompanied by progesterone. Bleeding follows cessation of the administration and then the substances are given again for some three to

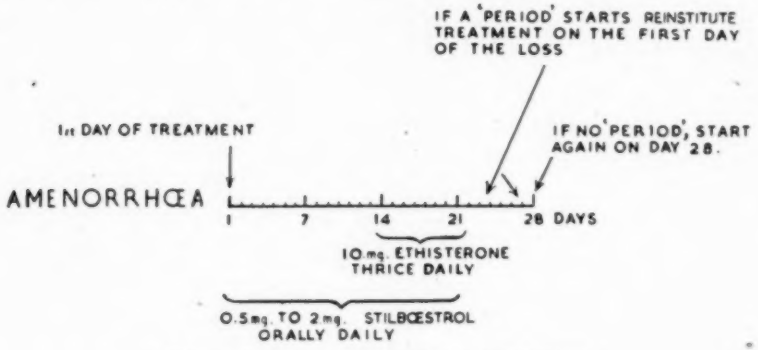
IF A 'PERIOD' STARTS REINSTITUTE TREATMENT ON THE FIRST DAY OF THE LOSS
1st DAY OF TREATMENT
IF NO 'PERIOD', START AGAIN ON DAY 28.
AMENORRHŒA
1
7
14
21
28 DAYS
10 mg. ETHISTERONE THRICE DAILY
0.5 mg. TO 2 mg. STILBŒSTROL ORALLY DAILY

FIG. 4.—Œstrogen administration in amenorrhœa.

four months. Treatment should then cease for a month to six weeks to see if regularity is established spontaneously.

Increased menstrual loss.—Œstrogens have no rôle in increased menstrual loss at the times of puberty or the climacteric. During adult life they are of use to a variable extent in the treatment of metropathia hæmorrhagica. This condition is variable in its response to treatment in different patients. Some may well be tided over by endocrine treatment or curetting. Others will derive little help and will welcome operation. Heavy flooding can usually be temporarily controlled by relatively large doses of œstrogens. Here the more powerful ethinyl œstradiol is most useful, and should be given in a dosage of 0.25 mg. two-hourly until relief is obtained, then followed by 0.25 mg. daily for a week. The alternative of stilbœstrol, 5 mg. at similar intervals, is more likely to be accompanied by nausea and vomiting. This treatment should subsequently be followed by the use of progesterone to avoid further hyperplasia of the endometrium. The progesterone is given on the lines suggested by Albright and by Bishop: ethisterone, 50 mg. daily for seven days, or by injection, 20 mg. on alternate days, up to four doses; and this is followed by a relatively normal period. The progesterone is then repeated a month later to forestall further menorrhagia.

Dysmenorrhœa.—Of all menstrual symptoms surely this is the one most difficult to assess. The variable factors of emotion, temperament, sensitivity

to pain, and stage of maturity have all to be considered. No wonder then that there is multiplicity of treatments. Psychological factors play a part both in patient and doctor. One is reminded of the saying of the psychologist who admitted that he found any method of treatment successful for a time until he himself had doubt of its efficacy.

There is a restricted scope for endocrine treatment. Sturgis and Albright (1940) showed that essential dysmenorrhœa was associated with menstrual cycles in which ovulation had taken place. It has also been shown that ovulation can be inhibited by œstrogens given in a large enough dosage. Hence, if the patient can be made to have a non-ovulatory cycle she will have relief of pain during the succeeding period. This can be accomplished by giving stilbœstrol, 1 mg. twice daily for the first fourteen days of the menstrual cycle. Although effective, the treatment should only be used intermittently and for the patient who fails to obtain adequate relief by other means, for if it is continued, inhibition of the pituitary may result. Thus it is a method useful for some specific occasion when a painful period is likely to coincide.

Climacteric symptoms.—By no means all women at the climacteric need replacement therapy of ovarian substances, but if the symptoms are such as to need it, œstrogenic treatment is very successful in controlling the hot flushes and other symptoms which may be attributed to the imbalance between the failing ovarian function and the temporary overactivity of the anterior pituitary. Long-continued treatment may be necessary, and the dosage should be carefully controlled to as low a level as possible. Stilbœstrol, 0.25 mg. or 0.5 mg., should be given daily, and the reaction of the patient assessed. Having found the optimum dosage, this should be maintained and then lowered a little after some weeks. It is a good plan to break the courses of treatment after some months and then start again if necessary. Large doses increase the risk of irregular and excessive bleeding with consequent worry as to its causation. In view of the very variable sensitivity of the menopausal patient to œstrogens, stilbœstrol is recommended as the standard substance rather than the very potent ethinyl œstradiol.

Vaginal inflammatory conditions.—Senile vaginitis and atrophic skin lesions round the vaginal introitus benefit from œstrogen therapy. This is best given locally in the form of a suppository (10,000 units of œstradiol benzoate) inserted into the vagina.

A similar form of treatment is useful in children with vulvovaginitis. Here a small suppository is used (1000 units) to raise the resistance of the vaginal epithelium.

THE USE OF ŒSTROGENS IN PREGNANCY

The best indication for the use of œstrogens in relation to childbirth is to suppress lactation, if this is necessary. It is important to start administration as soon as possible. Either stilbœstrol or ethinyl œstradiol may be used, the

latter being the more effective and less often producing toxic symptoms. It is given in dosage of 0.05 mg., two tablets twice daily for two days, then one tablet thrice daily for five days. Stilbœstrol is given in dosage of 5 mg., thrice daily. Secondary filling of the breasts may occur and must be watched for, and treatment must then be given again for a few days. Breast tension in cases of mastitis may also thus be relieved; here stilbœstrol, 1 mg.four-hourly, for a few days is all that is necessary.

It is now generally agreed that œstrogens are not effective in the induction of labour.

Following the views of the Smiths (1948) there has been much discussion within recent years of the use of œstrogens in abortion, toxæmia of pregnancy, and in the diabetic pregnant patient. It would appear at present that the use of massive doses of stilbœstrol in these conditions is not indicated unless further work establishes the logic of the treatment.

THE TREATMENT OF STERILITY

As has already been mentioned, œstrogens may be indicated in the patient who is anxious to conceive but suffers from spells of amenorrhœa. Occasionally, too, they may be useful if it has been proved that the cervical mucus is particularly viscous at the time of ovulation, or should biochemical tests of the endometrium indicate disorder of the glycogen metabolism.

THE TREATMENT OF CARCINOMA

Œstrogens would appear to have no scope in the treatment of genital carcinoma in the female; in fact, their use would appear harmful. However, mention must be made of their use in the treatment of carcinoma of the prostate, and of certain cases of carcinoma of the breast. It is scarcely within the province of the gynæcologist to discuss the indications and methods, both of which have been reviewed recently in *The Practitioner* (Nicholls, 1949; Paterson, 1950).

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THE PRESENT CLINICAL STATUS OF THE ANDROGENS

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THE androgens are substances which cause masculinization. They possess a steroid nucleus with ketonic or hydroxyl radicles at diametrically opposite positions in the nucleus, namely, at carbon atoms 3 and 17. They are formed in the testis, the ovary and the adrenal cortex. It has been demonstrated by a number of experiments that androgens are derived from the interstitial cells of the testis. The seminiferous tubules atrophy when the testicles are implanted into the abdominal cavity or are treated by a certain critical dosage of x-rays, and the animal becomes sterile, but the interstitial cells remain relatively unaffected and the secondary sexual characteristics do not regress. Conversely, certain specific poisons, notably pitch, and vitamin B deficient diets, destroy the interstitial cells, resulting in regression of secondary sexual characteristics, while the seminiferous tubules remain

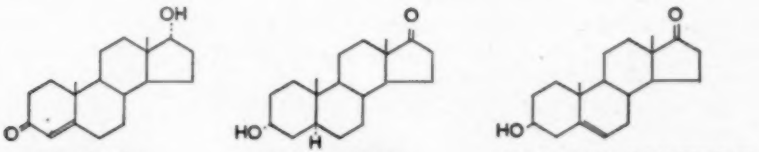

Fig. 1.

intact. The finding of androgens in other organs is an enigma. In the female the production of androgens by the ovary appears to be influenced by temperature. When an ovary is transplanted into the ear of a castrated male mouse or rabbit which is kept at ordinary room temperature, it will stimulate the accessory sexual organs which would otherwise involute. When the ovary is transplanted into the abdomen, however, it will fail to stimulate these organs, indicating that there is a higher rate of production of androgens in the ovary at lower temperatures. In both sexes androgens have been obtained from the adrenal cortex, but Reichstein has pointed out that they could have been formed there as a result of the isolation procedures employed.

It is not known therefore whether the androgens which have been isolated from the ovary and from the adrenal cortex are natural hormones of these organs or are simply excretion products of ovarian and of adrenocortical steroid metabolism which happen to be androgens by an accident of nature. In support of the latter it has been shown that administration of desoxy-

corticosterone to ovariectomized or to adrenalectomized animals causes a significant increase in the rate of excretion of androgens. Moreover, it is probably significant that the natural androgen of the testis, testosterone, which is a 3-keto, 17-hydroxy compound, is mainly excreted as a 17-keto, 3-hydroxy compound. The ketone and the hydroxy radicle are interchanged and it becomes indistinguishable from the 17-ketosteroids derived from the adrenal cortex. These relationships are shown in figure 1.

URINARY ANDROGENS AND 17-KETOSTEROIDS

It is important to distinguish between androgens and 17-ketosteroids. The former term refers to substances having a specific biological activity, and the latter to substances having a specific chemical characteristic. They have become almost synonymous in some circles, but this is quite wrong since many 17-ketosteroids have no biological activity, and certain androgens, notably testosterone, are not 17-ketosteroids. Biological assays were used for the earliest clinical investigations of androgen output, but they were elaborate and expensive. Cockerels were caponized and injected with androgenic material and the subsequent growth of the comb was measured. More recently, day-old chicks have been used and the material applied locally to the combs. With these methods it has been found that there is a close agreement between the concentration of androgen and of neutral 17-ketosteroids in human urine in health and disease. Attention has therefore been concentrated upon the more simple and accurate chemical procedures for the determination of 17-ketosteroids.

Various methods have been used for the determination of neutral 17-ketosteroids. In some centres a polarographic technique is used because it is sensitive and relatively rapid, but it requires elaborate apparatus, and in the great majority of laboratories some modification of Callow's method is in use. The modifications are numerous and the results obtained in different centres do not always correspond with one another. The Committee on Clinical Endocrinology of the Medical Research Council has therefore suggested that the method should be standardized, and has prepared a note in which the proposed standard method is described. This was published in the *Lancet* (1951), and copies are also available to anyone upon application to the Secretary.

Attempts have been made to increase the specificity of the assay. Callow isolated dehydro*iso*androsterone from the urine of patients with adrenal cortical tumours, but was unable to do so in patients without tumours. It is a 3(β)hydroxy ketosteroid, which is distinguished from the 3(α)hydroxy ketosteroids by the spatial relationship of the 3-hydroxy radicle to the angular methyl group at carbon atom 10. The (β) configuration is shown diagrammatically with a continuous line and the (α) configuration with an interrupted line (fig. 1). The 3(β)hydroxy-17-ketosteroids can be separated as a group from the 3(α)hydroxy-17-ketosteroids and measured. The pro-

cedure is more complicated than the determination of total 17-ketosteroids, but it is justified when an adrenal cortical tumour is suspected because it is then excreted in relatively higher concentration. Normally the ratio of (β) to total 17-ketosteroids is about 1:5 or 1:10, and it may be increased to 1:1 with tumours, but children with the adrenogenital syndrome associated with hyperplasia of the adrenal cortex, whose output of total 17-ketosteroids may

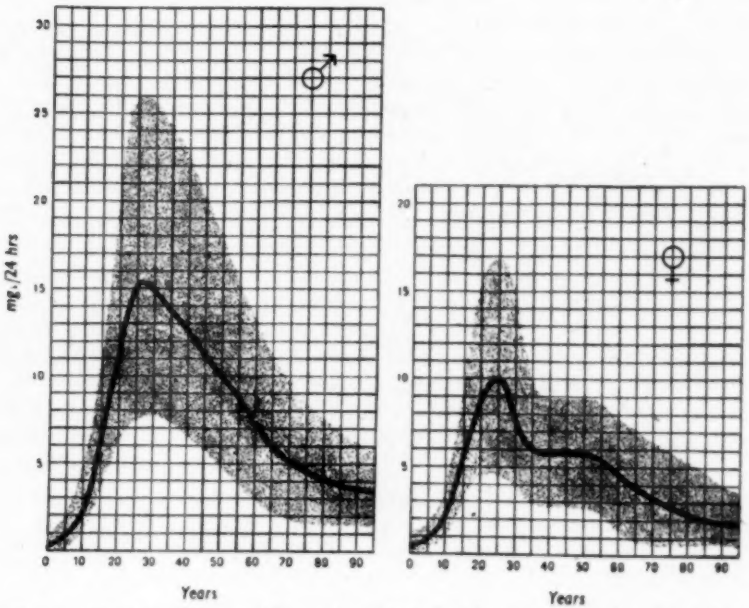

FIG. 2.—Neutral 17-ketosteroid excretions of 264 healthy people (Hamburger, 1948).

be very high, still commonly have a ratio of about 1:10. Recently, more specific assays have been developed for dehydro*iso*androsterone, but it is not yet established that these complicated procedures are justified by the additional clinical information obtained.

The determination of the urinary output of total neutral 17-ketosteroids is widely recognized as a useful procedure for clinical diagnosis and research. It is customarily measured against time, the urine sample being collected over a twenty-four-hour period. The output varies greatly with the age and sex. It is very low in children of both sexes and gradually increases until puberty. During adolescence it increases more rapidly in males than in females, and reaches a peak between the ages of twenty and thirty years. The level in mature females is about two-thirds of that of mature males.

Subsequently it declines gradually to about a quarter of the peak value in old age.

Normal ranges have been recorded by many workers, among whom there is good agreement about the general trend although their absolute values vary according to the methods which they have employed. Figure 2 represents the results of an examination of a large series of individuals by Hamburger (1948), in which 97 to 98 per cent. of his normal samples fell within the shaded area of the graph. His figures agree well with those of a smaller series examined by the standard Callow method.

The mean daily level of excretion is altered in a number of pathological conditions, especially of the pituitary gland, the adrenal cortex and the gonads. The principal use of the assay is for the differentiation of various types of adrenal cortical excess. Patients with *Cushing's syndrome* unassociated with an adrenal cortical tumour tend to excrete an amount of neutral 17-ketosteroids which is within the upper limit of, or slightly above, the normal range, but there is considerable variation between different individuals. Much higher values are generally found in the presence of adrenal cortical tumours. In women with hirsutism or virilism or the *adrenogenital syndrome* the values again tend to fall within the upper limit of, or slightly above, the normal range, in the absence of adrenal cortical tumours, but very high values up to one hundred times the normal are generally found when tumours are present. When the adrenogenital syndrome develops before puberty, however, and especially if there is marked precocious puberty or pseudohermaphroditism, values around ten times the normal are commonly found in the absence of adrenal cortical tumours. They may be much higher when tumours are present. The $(\alpha):(\beta)$ ratio is of the greatest value in the diagnosis of tumours in these cases. It is usually about 5:1 or normal in patients with hyperplasia and about 1:1 in patients with tumours of the adrenal cortex. Patients with tumours of the adrenal cortex which cause no endocrine disorders have a normal level of excretion of 17-ketosteroids.

In *Addison's disease* the level of neutral 17-ketosteroids is generally reduced to about one-third of the normal in both sexes, although occasionally it is undetectable in women. In pituitary insufficiency the level is very low in both sexes. Reference to figure 2 will show, however, that a value of one-third of the mean does not fall far below the shaded area, and since there is considerable variation in the level in different patients with pituitary and adrenocortical insufficiency, the level does not give a reliable guide to the presence or absence of these diseases, except when the clinical diagnosis is obvious. Moreover, in *anorexia nervosa*, a condition which is still sometimes confused with Simmonds' disease, there is often a moderately reduced level of excretion of 17-ketosteroids, so that the assay is of little assistance in differentiating these disorders.

The results of urinary assays have been reported on a relatively small number of patients with various *tumours of the testicles*. Several of these have

shown a slight increase in the level of excretion of 17-ketosteroids, but tumours of interstitial cells have been associated with very high levels. The results on patients with various *ovarian tumours*, including arrhenoblastomas, are conflicting. *Castrated and eunuchoid men* generally excrete less than half the normal amount and *eunuchoid women* about one-third, but no extensive series of values is available. There is some disagreement about the levels in ovariectomized women but most authorities have reported no appreciable change. The level of excretion of 17-ketosteroids is also affected in *thyroid disease*. It is moderately reduced in thyrotoxicosis and greatly reduced in myxœdema. Dorfman (1948) has made an extensive review of the literature on the chemistry and excretion of the androgens and related compounds.

Hitherto the data have been concerned with the total excretion of 17-ketosteroids during a period of twenty-four hours, but the excretion rate changes significantly in shorter periods of time. This variation is mainly due to the adrenocortical component, because it has been shown that the level is raised by treatment with the adrenocorticotrophic hormone. It is lower at night than during the day time, and rises appreciably under conditions of severe physical and mental exertion. It follows the changes in output of the adrenocortical hormones in stress: it has been shown to fall parallel with the reduction in the number of circulating eosinophil cells after major operations, and subsequently to rise to high levels with them during the phase which Selye calls 'counter-shock'. It is not, however, a sensitive test of adrenocortical function, and is likely to be superseded soon by direct determinations of water-soluble 3-ketosteroids or adrenocortical hormones in plasma.

ANDROGEN THERAPY

A number of preparations of androgens are available for clinical use and are sold under a variety of different trade names, but the principal chemical agents are the following: testosterone propionate in oily solutions and in crystalline suspensions for intramuscular injection; testosterone in pellets for subcutaneous implantation; and methyl testosterone in linguets for slow absorption under the tongue. The most economical form of treatment is pellet implantation, because pellets are very slowly absorbed and are effective for six to eight months. The usual dose is about 400 to 600 mg. The next choice is the injection of crystalline suspensions, which are effective for about a week and are given in doses of 25 to 100 mg. This form of treatment is tending to supersede the injection of oily solutions, which are given in doses of 5 to 25 mg., and have to be repeated daily or given two or three times a week. Methyl testosterone as linguets is the least economical but the most convenient form of treatment. It is usually given in doses of 5 to 50 mg. daily, but various workers have estimated that it requires between two and six times the intramuscular dose to produce the same effect when given sublingually. These substances are all powerful stimulants of secondary

sexual organs and of protein metabolism, but recently androstenediol has been introduced because it has little effect on the sexual organs but is a mild stimulant of protein metabolism.

The male.—Androgens are useful in the adult male castrate and eunuchoid for replacement therapy. They cause hypertrophy and pigmentation of the scrotum and penis, enlargement of the seminal vesicles and prostate, growth of pubic and facial hair, and deepening of the voice. They have been tried extensively for deficiencies of spermatozoa in cases of infertility, but results have been singularly disappointing; indeed, they are often regarded as inhibitors of spermatogenesis. Actually spermatogenesis is inhibited by the absence of androgens, but big doses depress pituitary gonadotrophic production and thus reduce spermatogenesis. Androgen treatment of impotence is usually disappointing as this is generally a psychological disorder. It has also been used for homosexuality, but male homosexuals have all the physical attributes of normal males so that treatment will exacerbate the sexual drive but not alter its direction, and it generally makes the condition worse. The whole subject of androgen treatment of the male has been extensively reviewed by Heller and Maddock (1947).

The female.—Androgen treatment has been used widely in the female. It is effective in the control of intractable uterine bleeding when this is coming from an endometrium of proliferative type, or in frank metropathia hæmorrhagica. The best method is to give massive doses of methyl testosterone orally, such as 25 mg. thrice daily, together with massive doses of oral progesterone (ethisterone), such as 60 mg. thrice daily for three or four days only. This nearly always stops bleeding immediately, but within two to four days the patient will often have a period of normal length, followed by a normal interval. The course should be repeated, starting on the first day of the next period, which will almost certainly be of normal duration and be followed by another normal interval. It should be repeated with each period for some months, the dose of testosterone then being gradually reduced and later the dose of ethisterone reduced. Relapses are common but the treatment is simple, and the alternative in these intractable cases is usually hysterectomy or a radium menopause, which should be avoided if at all possible in young women. Androgen treatment never causes virilism when given over such short periods of time, even in adolescent girls. This form of therapy is disappointing in patients with excessive bleeding from a secretory type of endometrium, but they sometimes respond to androgens alone or androgens combined with œstrogens. Generally speaking, these cases are difficult to control with any form of hormone treatment. Androgens have been used with some degree of success in endometriosis, in dysmenorrhœa, and in premenstrual tension and œdema. They are effective in increasing libido in women, and they have been recommended for the treatment of menopausal symptoms in conjunction with œstrogens when the latter alone cause uterine bleeding. They reduce the pain in mastodynia and adeno-

fibrosis of the breasts, but therapy has to be continuous and is generally impracticable for any length of time because of the virilism which is induced. Androgen therapy in the diseases of women has been fully reviewed by Carter, Cohen and Shorr (1947).

The use of androgens for their effect on metabolism is interesting. They are protein-anabolic and cause an increase in body weight, and particularly in muscle mass and skeletal growth, but they cause the epiphyses to join with the diaphyses and thus arrest growth after an initial spurt. They are more effective in the treatment of pituitary and ateleiotic dwarfs than is growth hormone itself. They cause a remarkable improvement in patients with Simmonds' disease, and sometimes appear to assist patients with Addison's disease when given in conjunction with adrenocortical hormones.

Considerable success has been claimed for the treatment of *breast cancer* and its metastases with androgens. They are given in massive doses continuously and indefinitely. Adair (1949) recommended 200 mg. of testosterone propionate daily, and claimed a similar degree of success to that obtained by radiotherapy, but this treatment is almost prohibitively expensive. It often causes a remarkable reduction of bone pains and contraction of bony metastases on radiological examination, but for the present it must be regarded as an experimental procedure.

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THE ENDOCRINOLOGICAL ASPECTS OF OBESITY

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Only a small percentage of patients with obesity show any evidence of a recognized endocrine disturbance, and in these, obesity is not usually the only manifestation of such a disorder. Well-known examples of endocrine disease in which obesity is, or may be, a prominent feature are Cushing's syndrome with its plethora, purpuric striæ, hypertension, hyperglycæmia, amenorrhœa and osteoporosis; chromophobe adenoma of the pituitary gland and craniopharyngioma, in both of which headache is usually present and there is radiological evidence of the lesion; eunuchism and eunuchoidism with its small, atrophic testes and lack of secondary sexual characteristics; and some cases of myxœdema. The vast majority of obese patients do not fall into any of such categories, but suffer from 'simple' obesity.

Gluttony was thought to be a common cause of obesity, but this view is now being abandoned: (1) because experience has shown that many obese persons do not eat more than normal subjects, and (2) because patients who indulge in excessive consumption of food may be suffering from a pathological hunger akin to the pathological thirst of diabetes insipidus. Although the medical practitioner in referring an obese patient to the consultant may suggest that there is some endocrine cause, the truth is that in simple obesity it is not known what gland is at fault or in fact whether the condition is even due to an endocrine disorder. In view of this doubt the etiological relationship to obesity of those ductless glands which may possibly be incriminated will be discussed.

THE THYROID GLAND

The essential action of the thyroid hormone is to stimulate metabolism, and through the resulting increased expenditure of energy it indirectly brings about loss of fat from the organism. On the other hand, deficiency of thyroid hormone does not necessarily cause an increase of body fat as a reversal of this process; in fact, thyroidectomized rats are found to possess much less fat several months after the operation than the control animals (MacKay and Sherrill, 1941). On the clinical side, Plummer (1940) observed that of 200 patients with myxœdema only a small number were significantly obese; the loss of weight in myxœdematous persons resulting from thyroid medication is due largely to the elimination of excess of fluid. Numerous investigators have found that in the vast majority of obese persons the basal metabolic rate is within normal limits. Williams (1948), who determined the level of the protein-bound iodine of the plasma in 24 obese patients, concluded that an alteration of thyroid function does not have much etiological significance in obesity. This opinion is in agreement with the

accumulated evidence, and the generally held view that obesity is often due to hypothyroidism is a misconception.

THE ADRENAL CORTEX

Hyperfunction of the adrenal cortex, whether this be due to a tumour or to simple hyperplasia, gives rise to various clinical manifestations and may be accompanied by gross obesity. Obesity occurs in children with *adrenal cortical tumours* and in *Cushing's syndrome*, some cases of which are due to a primary disorder of the adrenal cortex, and others to excessive secretion of the adrenocorticotrophic hormone of the anterior lobe of the pituitary gland, resulting in secondary adrenocortical hyperfunction. The hormones which produce most of the clinical features of Cushing's syndrome belong to the corticosterone group of substances (11-oxysteroids), of which cortisone is an example. The questions which arise are, first, whether one or more of the corticosterones are responsible for the obesity of Cushing's syndrome and, secondly, if this be true, whether some cases of simple obesity can be ascribed to one of these substances. An action common to a number of the corticosterones is the production of glycosuria and hyperglycæmia, which is brought about, it is suggested by Albright (1943), by their converting into glucose certain amino-acids which would otherwise be built up into protein. Albright (1943) has further suggested that the obesity associated with this type of adrenal tumour may be due to the subsequent conversion of glucose into fat. Kendall (1945) reported a marked increase in the percentage of body fat in mice by administering either corticosterone or 11-dehydrocorticosterone, but he found that cortisone had little effect on the body fat. From the available evidence it is probable that the obesity of Cushing's syndrome is due to the excessive secretion of certain corticosterones.

The second question, namely, whether *adrenocortical hyperfunction* is sometimes the cause of simple obesity, remains unanswered, and the suggestion which I put forward that such a disturbance may be responsible for some cases is purely conjecture. All clinicians have observed patients who do not demonstrate the full symptom-complex of Cushing's syndrome, but who present obesity in association with hyperglycæmia and hypertension only, or with merely one of these disturbances. In fact, there appear to be various gradations of clinical pictures from the complete Cushing's syndrome on the one hand, to simple obesity on the other. In these cases, apart from Cushing's syndrome, there is no tangible evidence of cortical hyperfunction, but even so its existence is not beyond the bounds of possibility.

THE ANTERIOR PITUITARY GLAND

Hypopituitarism is often mentioned as a cause of obesity. Let us examine the evidence. It is a well-known clinical fact that obesity may arise in patients with a chromophobe adenoma or a craniopharyngioma, either of which tumours may destroy or seriously damage the pituitary gland and cause

symptoms of hypopituitarism. The belief that anterior pituitary deficiency is a cause of obesity dates from the original descriptions of Babinski in 1900, and of Fröhlich in 1901, of obesity occurring in combination with sexual infantilism in adolescents with a pituitary tumour (probably a craniopharyngioma). This hypothesis was strengthened by the results obtained in the early experiments on partial ablation of the pituitary gland in which the animals so treated became obese. Smith (1926), however, failed to produce obesity in his animals when he removed the anterior lobe without damaging the tuber cinereum and the hypothalamus; this work has been confirmed by other investigators. From the experimental evidence it is established that when obesity arises after hypophysectomy it is due, not to pituitary insufficiency, but to hypothalamic damage, and it appears that this damage must have been inadvertently inflicted by the earlier investigators.

Clinically, obesity is more prone to occur with a *craniopharyngioma* which lies above the sella turcica than with a chromophobe adenoma which arises within the gland, and obesity is unusual when the anterior lobe is damaged or destroyed by a non-functioning lesion which is confined within the sella. The evidence strongly suggests that when a chromophobe adenoma or a craniopharyngioma causes obesity it does so by damaging centres in the hypothalamus. In view of these arguments, which appertain to a demonstrable lesion, there is little support for the conception that obesity is due to functional hypopituitarism in which no lesion can be discovered.

The question now arises whether simple obesity may be caused by overactivity of certain elements of the anterior lobe. The recognized syndromes caused by *hyperpituitarism* are acromegaly, gigantism, and some cases of Cushing's syndrome. Obesity is not a usual feature of acromegaly and gigantism, and as these conditions are due to excessive secretion of growth hormone it is therefore unlikely that excess of this substance can cause obesity. Attention has been drawn to the production of obesity in Evans's rats treated with growth-promoting extract of the anterior lobe and, whilst its development may not be due to growth hormone itself, it is possible that some other pituitary hormone in the extract may have been responsible.

Whether or not simple obesity may be caused by hyperpituitarism is debatable. There are three periods of life when obesity is prone to develop —at puberty, after pregnancy, and after the menopause. *At puberty* there is an awakening of anterior lobe activity, essential for statural and sexual development; *after the menopause* there is a marked fall in œstrogen secretion by the ovaries, and consequently the inhibitory action of œstrogen on the anterior lobe is removed and the secretion of pituitary gonadotrophin is increased. There is no evidence, however, that excess of gonadotrophins causes obesity; if obesity arising at these periods is due to hyperpituitarism one must postulate excessive production of some other hormone (ACTH).

During *pregnancy* there is hyperfunction of the anterior lobe and of the adrenal cortex, hyperfunction of the latter being due to increased secretion of adrenocorticotrophic hormone; the urinary excretion of adrenal corticoids

is increased (Venning, 1946). If post-pregnancy obesity is due to hyperpituitarism, we are again driven to a consideration of the adrenocorticosterones as the possible direct cause of the obesity, and must postulate a continuation of pituitary and cortical hyperfunction after pregnancy in these patients. One of the difficulties, however, of explaining post-pregnancy obesity as being due to hyperpituitarism is, as Sheldon (1949) has pointed out, the variable time of onset of the obesity after pregnancy.

THE HYPOTHALAMUS

When discussing the endocrinological aspect of obesity we should not omit reference to the hypothalamus, for it has been established that this structure controls certain functions of the anterior and posterior lobes of the pituitary gland. Mention has already been made of the observation that obesity does not develop after hypophysectomy unless the hypothalamus is damaged during the operation. Bilateral lesions placed in the hypothalamus and not involving the pituitary gland cause marked obesity in rats (Hetherington and Ranson, 1939, 1940). The gain in weight begins immediately after the operation and is associated with a voracious appetite. Hetherington and Ranson (1942) showed that removal of the pituitary gland six to ten days after the operation on the hypothalamus made no difference to the subsequent development of obesity. From this they concluded that hypothalamic obesity cannot be explained in terms of a disturbance of pituitary activity, and they found that the production of obesity was due to the destruction of pathways which travel from the hypothalamus down the brain stem and which do not concern the pituitary gland at all.

Clinically, obesity may arise as a sequel of diseases such as encephalitis and meningitis, presumably through hypothalamic damage, and the association of obesity with *pituitary tumours* (chromophobe adenoma and craniopharyngioma) is due to extension of the growth into the hypothalamus. The question arises whether obesity may occur as a result of disordered function of centres in the hypothalamus in the absence of any clinical evidence of an organic lesion. It is well known that a rapid increase of weight may follow *psychological disturbances*, more especially chronic unhappiness, and it has been suggested that in these cases it is caused by impulses from the cortex acting on centres in the hypothalamus which control the metabolism of fat (Shorvon and Richardson, 1949). The onset of obesity as a result of an emotional upset is thus analogous to the production of amenorrhœa through the same cause: in the latter case, impulses from hypothalamic centres which control the secretion of pituitary gonadotrophins and regulate ovarian function are inhibited. Not uncommonly obesity of this type is accompanied by amenorrhœa, and occasionally by other evidence of hypothalamic dysfunction, such as drowsiness. Both the experimental and clinical evidence suggest that the hypothalamus contains a centre for the regulation of fat metabolism and that some cases of obesity are due to a disturbance of this centre, but the mechanism of its action is unknown.

Water retention may be present in obese subjects and may sometimes be demonstrable by pitting œdema. Associated with the retention of water there may be diminished excretion of sodium chloride. Verney (1947, 1948) has shown that water diuresis in the dog can be inhibited by subjecting the animal to emotional stress or to muscular exercise, which itself engenders emotional stress. He suggested that this inhibition is due to increased secretion of the antidiuretic factor of the posterior pituitary gland, brought about by the excitation of the supra-optic nuclei of the hypothalamus which control posterior pituitary function. Verney's experiments are of importance, for they lend support to the conception that obesity associated with water retention may be due to disordered function of the hypothalamus.

THE GONADS

From the earliest times castration has been practised in order to fatten livestock, and this is now being achieved in cockerels by implanting pellets of stilbœstrol, which induces testicular atrophy. It would thus appear that the fattening process is due to deficiency of gonadal secretion. In clinical medicine, however, gonadal deficiency is often unassociated with obesity. Obesity occurs hardly more frequently in eunuchism and in eunuchoidism than in normal men (Moore, 1935), and it is not a feature of ovarian infantilism in which there is failure of ovarian development. Whilst obesity arises not uncommonly at the time of the menopause, treatment with œstrogen or with progesterone is ineffective in reducing the excess of fat, and the administration of testosterone is similarly ineffective in the treatment of obesity associated with eunuchoidism. There is no evidence that gonadal deficiency plays any part in the etiology of simple obesity.

THE PANCREAS

Obesity may be caused by *hyperinsulinism* due to a tumour or to hyperplasia of the islets of Langerhans. This condition, however, is rare, and although an increased carbohydrate tolerance is sometimes present in obese patients, there is no clear evidence that obesity in these cases is due to excessive secretion of insulin. On the other hand, obesity is common in *diabetes*; the adrenal view of this association has been discussed. The obesity often precedes the glycosuria, and Lawrence (1941) has suggested that in these cases the first disturbance is a mild symptomless hyperglycæmia which is responsible for the obesity. Lawrence (1946) later postulated as a cause of diabetic obesity an excess of a hypothetical lipopexic (fat-fixing) hormone or a diminution of a lipocatabolic hormone.

DIAGNOSIS

The differentiation of simple obesity from that due to a demonstrable endocrine cause usually presents no difficulty, because in the latter instance there are generally in addition other features characteristic of a particular syndrome or disease. Inquiry should be made into the familial history and

the past history of obesity, the relationship, if any, of the obesity to pregnancy, the amount of food ingested, the time and rapidity of onset of the obesity, and the presence of other relevant symptoms, such as headache, visual disturbances, and sexual function. When the development of obesity is rapid over a period of twelve months or so in adolescents and young adults the pituitary fossa should be examined radiologically to determine the existence of a pituitary tumour; in my experience the rapid onset of obesity may be the first symptom of a craniopharyngioma and may be unaccompanied by headache or subjective visual disturbances, although a defect may be found in the visual fields. When obesity is accompanied by delay in the onset of puberty the pituitary fossa should also be x-rayed for the presence of a craniopharyngioma, but the vast majority of these cases are suffering from simple obesity and their sexual development proceeds in due course.

ENDOCRINE TREATMENT

It will be appreciated that there is as yet no endocrine treatment for this condition, with the possible exception of the administration of thyroid in certain cases. Pituitary extracts have no place in the treatment of obesity, adrenocortical hormones are not indicated for obvious reasons and the sex hormones have little or no effect on obesity, even when it is accompanied by gonadal deficiency.

SUMMARY

There is no evidence that simple obesity, that is, obesity which is not associated with any recognized endocrine syndrome, is due to hypopituitarism, hypothyroidism, gonadal deficiency or hyperinsulinism. The possibility that some cases may be caused by overactivity of the anterior pituitary-adrenocortical system and others by a disturbance of centres in the hypothalamus is discussed. Endocrine therapy, with the possible exception of thyroid in certain cases, has at present no place in the treatment of simple obesity.

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DRUGS USED IN OPHTHALMOLOGY

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Drugs that are applied locally to the eye can be studied under three main headings:—(1) Drugs used in the treatment of inflammatory conditions of the external eye and appendages. (2) Drugs having an action upon the tissues inside the eye. (3) Anæsthetics.

BATHING OR IRRIGATION OF AN EYE

When anyone has a sore eye, the tendency is to resort to eye bathing. In certain diseases this is a necessary part of treatment, but it is overdone. If there is any irritant which should be washed away, then bathing is indicated, and again, if the eye is very painful, hot bathing can be soothing and comforting. In acute conjunctivitis there is much pus about the borders of the eyelids and in the fornices. To bathe the eye properly the patient should be recumbent.

Articles required in hospital: a towel laid upon the patient's chest, another towel encircling the head, a container with the fluid that is to be used, an undine, kidney basin, and cotton-wool. The undine is filled with the fluid, the kidney basin is pressed against the cheek on the same side as the eye to be bathed, and the patient directed to tilt the head a little towards that side. A little of the fluid is run from the undine on to the back of the hand of the person who is to do the bathing. If the fluid is too hot for the back of the hand, it is certainly too hot for an eye. The eyelids are separated, using the thumb and first finger of the left hand, and the fluid is directed into the eye from a height of about 6 inches. The patient is told to look successively upwards, downwards and to the right and left. The fluid passes over the eye and is caught in the kidney basin. The lids are then wiped dry with cotton-wool.

In the home, such utensils as undines or kidney basins are not usually available, so something else has to be substituted. For the undine, a cream jug or old teapot is quite suitable, and instead of the kidney basin a small pudding dish can be used. In an emergency, balls of cotton-wool can be dipped into the hot lotion and the fluid squeezed into the eye.

Hot bathing.—In a painful, inflammatory condition of the eyeball, such as iritis or corneal ulceration, moist heat applied to the eye increases the blood supply to the eye, and often increases the action of the drug used as drops in the treatment of the condition.

For hot bathing of an eye a bowl is filled with boiling water, cotton-wool is wrapped round the end of a wooden spoon or piece of wood, the patient is seated in front of the bowl, and the handle end of the spoon is taken in the hand corresponding to the sore eye. The end of the spoon, which is wrapped with the wool, is then dipped into the boiling water and is approached close to the closed eye, the steam and heat being allowed to act upon the eye. When the wool has cooled sufficiently it is pressed on to the closed eyelids. This is repeated for about fifteen minutes. No drug need be mixed with the water, as it is entirely the moist heat that is being used therapeutically.

Another form of moist heat that can be applied to an eye is a fomentation

in the treatment of a stye. This is made in the usual way with pink lint, and held in position with cotton-wool, oiled silk, and a bandage.

DRUGS USED AS LOTIONS

No drug can be used in sufficient strength in the form of a lotion to have any bactericidal effect upon pathogenic organisms in the vicinity of the eye. When an eye is bathed it is only the action of the fluid washing away pus, organisms or foreign material which need be expected. All kinds of substances have been used for bathing the eyes, but I shall only refer to three:—

(1) *Normal saline* at a temperature of 100° F. (37.8° C.)—i.e., slightly warmer than the body tissues. In hospital an exact concentration of 0.9 per cent. can be made. In the home a teaspoonful of salt to a pint of lukewarm water is near enough.

(2) *Boric lotion.*—A teaspoonful of the crystals is used to a pint of lukewarm water.

(3) *Sodium bicarbonate lotion.*—This is used in the same strength as the other two but for a slightly different purpose. In the case of blepharitis in a schoolchild the borders of the eyelids are very crusted, and before any drug will act the crusts must be removed. Small pieces of cotton-wool are dipped into lukewarm lotion and pressed against the closed eyelids. The eyelids are then dried with a fairly rough towel, when most of the crusts will thereby be emoved.

DRUGS USED AS EYE DROPS

Up to the introduction of the sulphonamides and penicillin, silver drops were used extensively. Silver nitrate, 1 per cent., is still used as prophylactic treatment for ophthalmia neonatorum, but in the Eye Department of the Royal Infirmary in Aberdeen, except for this condition, it is never prescribed now. *Argyrol*, however, is occasionally used in patients who are sensitive to the action of penicillin or sulphacetamide. The prescription is:—

Argyrol drops ..... 10 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to both eyes twice daily.

I prefer to prescribe all eye drops in the percentage form. The prescription is easy to remember and easy to write. A 1 per cent. solution is approximately 4 grains (0.25 g.) of the drug to 1 ounce (28.5 ml.) of water.

If silver drops are used over a prolonged period permanent staining of the conjunctiva takes place, the colour of the inside of the eyelid and white of the eye turning a dirty grey. The condition is known as argyrosis.

Zinc sulphate has been used as drops for many years in the treatment of angular conjunctivitis and for epiphora in the aged. The prescription is:—

Zinc sulphate drops ..... 0.25 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to each eye twice daily.

Eye drops should always be dispensed in a bottle which has the dropper as part of the cork. In the usual household the dropper, if separate from the

bottle, is often kept in unhygienic places. 'Pipette bottle' should be written on the prescription, as otherwise the chemist will not be paid for this special bottle.

To put a drop into an eye, some of the fluid is sucked up into the pipette. A drop will be seen to hang from the tip of the pipette. The lower eyelid is pulled down with the thumb of the other hand, the inner surface of the lower eyelid is touched with the drop hanging from the tip of the pipette, and the eyelid released. The fluid must not be squirted in by pressing the rubber part of the pipette as, if this be done, the fluid cannot be accommodated in the eye and will run down the cheek. The patient should be discouraged from attempts to put drops into the eye personally.

With the above exceptions, all cases of conjunctivitis are now treated either with sulphacetamide or penicillin. The strength of *sulphacetamide* is 10 per cent., except in the treatment of ophthalmia neonatorum, when it can be used in 30 per cent. strength. The prescription is:—

Sulphacetamide drops ..... 10 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to both eyes twice daily.

Penicillin is prepared as follows:—

Penicillin drops B.P.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to both eyes twice daily.

In susceptible individuals both these drugs can, on occasion, cause irritation, so, if on the following day the eyelids are red and swollen, the conjunctivitis is not worse, but the patient is suffering from drug irritation, and the drops must immediately be stopped and argyrol substituted.

OINTMENTS

In the treatment of blepharitis after the crusts have been removed an ointment is rubbed into the roots of the eyelashes:—

Sulphacetamide ointment ..... 2.5 per cent.
Send small tube.
To be applied to the eyelids twice daily.

To keep the eyelids from sticking together through the night this ointment can be used, or petroleum jelly, cold cream or boric acid ointment:—

Boric acid ointment B.P.
Send small tube.
Apply to the eyelids at night.

An ointment that has been used for generations in the treatment of blepharitis in children is known by the layman as golden eye ointment. It can still be used for children, but on no account for adults, as it will increase the redness of the borders of the eyelids. The prescription is:—

Dilute yellow mercuric oxide ointment B.P.
Send 120 grains (8 g.).
Apply to the borders of the eyelids at night or insert into the eye with a glass rod.

The latter method is used for phlyctenular conjunctivitis. If the cornea be invaded, atropine can be combined. The prescription would then be:—

Dilute yellow mercuric oxide ointment with atropine.... 1 per cent.
Send 120 grains (8 g.).
To be inserted into the eye with a glass rod.

To insert ointment into an eye using a glass rod, first dip the point of the rod into the ointment, separate the child's eyelids at the external canthus, using the thumb and index finger of the left hand. Place the point of the rod with the ointment in the lower fornix. Release the eyelids, and the child will immediately squeeze them together. Withdraw the rod horizontally, leaving the ointment inside the eyelids.

MYDRIATICS

We now come to the drugs that have a specific action upon the pupil of the eye. The first group are called mydriatics. If the drug also paralyses accommodation it is called a cycloplegic. All cycloplegics are mydriatics, but not all mydriatics are cycloplegics, e.g. cocaine and adrenaline.

Atropine.—Atropine is derived from the belladonna plant and will act in a dilution of 1:500,000. One drop of a 1 per cent. solution inserted into the eye will dilate the pupil in twenty minutes, and it will remain dilated for several days. It acts upon the myoneural junction of the parasympathetic nerve and, in the case of the pupil, paralyses the sphincter muscle. The pupil is then dilated by the pull of the dilator muscle and the action of the elastic fibres in the stroma of the iris. In the treatment of a disease such as iritis, when it is desirable that the pupil be quickly dilated and left dilated over a prolonged period, atropine is the drug of choice. It can be used every quarter of an hour until the pupil is dilated, and afterwards one drop instilled twice or three times a day. The prescription is:—

Atropine sulphate drops ..... 1 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to the eye twice daily.

It is advised that the frequency of application of the drops be increased rather than the strength. As atropine is also a cycloplegic, the inflamed and painful eye is put at complete rest. Atropine can also be used to keep the pupil semi-dilated in a case of cataract when the opacities are central, one drop of a 0.25 per cent. solution twice weekly being required. It can also be used in the treatment of squint. To estimate the refraction, one drop of a 1 per cent. solution is put into both eyes twice a day for three days. If the squint is still present after the child has worn the glasses for three months, a drop of 1 per cent. atropine can be put into the straight eye twice weekly. This forces the child to use the squinting eye for near work. To make a fundus examination, or to estimate the refraction in non-squinting individuals, atropine should not be used, as the prolonged action incapacitates the patient unnecessarily.

The cleaning of atropine pipettes.—Great care has to be exercised in the cleaning and sterilizing of pipettes that have been used for atropine. Boiling them in a sterilizer is not sufficient. Washing the pipettes below a running tap is first required so as to get rid of the atropine before placing the pipettes in the sterilizer. Nothing is more exasperating to the surgeon than to see a dilated pupil when a mydriatic has not been prescribed—nearly always it is due to a contaminated pipette being used.

Atropine irritation.—Atropine, if used over a long period, is liable to cause

irritation of the eyelids. They can swell and turn red to an alarming degree. Atropine must at once be stopped and another drug substituted. If atropine is given to such a patient at any future date a single drop will cause irritation, so *atropine irritation* should be written in red ink on the patient's case history sheet. The treatment for atropine irritation, in addition to stopping the drug, is the application of zinc and castor oil ointment to the eyelids. Antihistamine drugs have no effect. Occasionally I have found that if the ointment is substituted for the drops, irritation does not follow. This is due possibly to the ointment remaining in the eye and not running down the cheek. It might also be due to the fact that the atropine in the ointment is the pure alkaloid, and not sulphate as is present in the drops.

Homatropine.—Homatropine has the same action as atropine but does not act for so long, the eye returning to normal within twelve hours. It is combined with cocaine to hasten and increase its action. The pupil is fully dilated in half an hour, and cycloplegia is also practically complete and remains so from one to two hours. 'H. and C.', as it is called, can be used to estimate the refraction, even in a child, if a squint is not present. The result is just as accurate as with atropine; 0.50 is deducted from the correction instead of 1, as is the case when atropine is used. If the child has a squint, and the examination has to be done the same day, the correction can be given without any deduction. In adults, a watery solution of 2 per cent. each of homatropine and cocaine is used:—

Homatropine	2 per cent.
Cocaine	2 per cent.

Send ½ fl. oz (14 ml.); for surgery use.

For children I prefer the drug to be made up in castor oil :—

Homatropine	2 per cent.
Cocaine	2 per cent.
Castor oil	to 1 fl. oz (28.5 ml.)

For surgery use.

These drops should never be prescribed for a patient by way of treatment, as the cocaine has an injurious effect upon the corneal epithelium. They can, however, be used by the surgeon to dilate the pupil in a case of iridocyclitis when there is also a rise of tension, and also in the case of a red eye after a foreign body has been removed.

If 'H and C.' has been used to dilate the pupil so as to make a fundus examination in a patient over middle age, a drop of eserine, 1 per cent., should always be put in before the patient is allowed to leave.

A drop of 'H. and C,' in oil is easily inserted. A glass rod with a small ball on its tip is used or a metal wire with a flattened point. The rod is dipped into the oil, both lower eyelids are pulled down simultaneously by using the small finger and thumb of the same hand, the conjunctival edge of the eyelids are then quickly touched with the point of the rod, and both lids released at the same time. If one lid be touched and released the eye will nip, and it will be much more difficult to get the drop inserted into the other eye.

Only one application is required, and so small a quantity of oil is used that there is no difficulty in doing a retinoscopy one hour later.

Cocaine.—This is an anæsthetic and also a mydriatic. Its action is stimu-

lation of the sympathetic nerve. (It has no action upon an eye that has had a sympathectomy done, the pupil, in fact, becoming slightly smaller instead of larger.) It is therefore used diagnostically in a case of suspected Horner's syndrome. It has no cycloplegic action.

Adrenaline.—Adrenaline is a mydriatic but its action is entirely different from that of atropine. If a drop be instilled into the normal eye the conjunctiva is blanched, but no dilatation of the pupil takes place because the drug is not absorbed. If it be combined with cocaine, however, dilatation takes place. It acts by stimulating the sympathetic nerve which activates the dilator muscle in the iris.

Hyoscine (*scopolamine*).—Hyoscine has the same action as atropine but is not so powerful and is used only in cases in which there is atropine irritation. It is given in a 1 per cent. solution.

Mydricaine.—Mydricaine is a combination of atropine, cocaine, adrenaline, and a preservative. It is used to break down posterior synechiæ in cases of recurrent iritis. It is given as a subconjunctival injection, and is made up in ampoules ready for use.

Lachesine (1 per cent. solution).—This synthetic mydriatic is a substitute for atropine in cases of atropine irritation.

MIOTICS

A miotic is a drug which contracts the pupil. It is given to counteract the effect of 'H. and C.' after refraction estimation and fundus examination, and in the treatment of glaucoma.

Eserine, 1 or 0.5 per cent. solution, contracts the normal pupil in twenty minutes. For the treatment of chronic glaucoma, if operation is refused, it is prescribed in 0.5 per cent. strength, one drop to the eye twice daily:—

Eserine drops ..... 0.5 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to the eye twice daily.

In the treatment of acute glaucoma it can be instilled every fifteen minutes until the pupil is pin-point in size. If the pain is very severe and the tension high, a retrobulbar injection of 2 ml. of planocaine 1 per cent., with 4 drops of adrenaline 1:1000 solution, can be given. This often works like a charm. The pain goes immediately, the tension is reduced, and the cornea clears. If eserine now be instilled it will be found to act and to control the tension until operation can be performed. Eserine acts by preventing the breaking down of acetylcholine at the myoneural junction. It can cause irritation similar to atropine irritation, but not so severe.

Pilocarpine.—Pilocarpine is a miotic which acts directly upon the circular muscle of the iris. It is not so irritative or so powerful as eserine, but is preferable in cases of early chronic glaucoma. After use it does not cause supra-orbital pain as is often complained of by patients using eserine. The prescription is:—

Pilocarpine drops ..... 0.5 per cent.
Send ½ fl. oz. (14 ml.); pipette bottle.
One drop to both eyes twice daily.

ANÆSTHETICS

The drug used for surface anæsthesia of the eyeball in Aberdeen is cocaine in a 3 per cent. solution. We have found it reliable, efficient, and poisoning from its use has been so rare that it can be ignored completely. For the removal of a foreign body from the cornea two drops at five-minute intervals is all that is required. After the foreign body has been removed a drop of sulphacetamide drops, 10 per cent., is given as a prophylactic. For the incision of a meibomian cyst, a 1 ml. injection of 1 per cent. procaine hydrochloride is given into the vicinity of the cyst, in addition to the cocaine drops.

Plastic operations on the eyelids, unless extensive and requiring skin grafts, can be done painlessly with 1 per cent. procaine hydrochloride.

A cataract operation is preceded by the instillation of one drop of 'H. and C.' thirty minutes before the operation, followed by one drop of 3 per cent. cocaine every five minutes. With the last drop of cocaine one drop of adrenaline 1:1000 solution is given. When the patient is on the table a retrobulbar injection of 2 ml. of 1 per cent. procaine hydrochloride, with three drops of adrenaline 1:1000 solution, is given. This renders the eyeball anæsthetic and makes it slightly more prominent, which allows the corneal incision to be made more easily in districts where hypermetropia is the rule.

To give a retrobulbar injection the lower eyelid is cleaned with spirit or flavine. The edge of the lower orbital margin is felt for, and the patient is told to look upwards. The point of the narrow-bored 3-inch needle is inserted through the skin of the lower eyelid just clear of the orbital margin and in line with the external canthus. The needle is pushed firmly and steadily inwards and medialwards, just clearing the eyeball. It will be felt passing through the inferior rectus and entering the muscle cone. It is better to withdraw the needle about an ⅛ of an inch to make sure that it is not in a blood vessel, and the 2 ml. of solution is then slowly injected.

A retrobulbar injection is given: (1) previous to a major eye operation; (2) in the treatment of acute glaucoma; (3) to render a painful blind eye permanently anæsthetic.

For the latter condition, in addition to 1 ml. of procaine hydrochloride and three drops of adrenaline, 0.5 ml. of 95 per cent. alcohol is given. The needle is inserted in the usual way and the 1 ml. of procaine hydrochloride given. The syringe is then removed from the needle, which is left in position; 0.5 ml. of 95 per cent. alcohol is then drawn into the syringe, which is re-attached to the needle and the injection slowly given. Anæsthesia immediately takes place and is said to last for six months, but I have found it to last much longer. In fact, in the case of very old people the injection seldom has to be repeated.

CONCLUSION

It is not claimed that all the drugs used in ophthalmology have been mentioned but, provided the diagnosis is correct, sufficient have been described to treat rationally any pathological eye condition that may be encountered in general practice.

ASTHMA AS A STRESS REACTION: ITS DIAGNOSIS AND TREATMENT

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Γνῶθι σεαυτόν

These words were inscribed in the temple at Delphi. They are quoted by Juvena in his Satires (9:27) 'From the gods comes the saying "Know thyself"'.

Some evidence will be set forth in this article for the hypothesis that bronchial asthma is one of the forms of bodily reaction to stress. In reviewing the results of psychological treatment in the patients discussed, I saw that those who did well had more insight, after their treatment, than those who did badly. They had learned that their asthmatic attacks were not a mysterious malady sent to them by the malice of Fate, but a physical response to certain feelings which could be recognized and understood. They knew something of the events in life which might arouse such feelings, and how these could be circumvented or, better, controlled. In short, they had striven to obey the divine injunction—'know thyself'.

Insight of itself does not, of course, account for the change in those who did well. It is one aspect of this change. The patient who recovers does not only think differently, he also acts and feels differently. His recovery is reflected in his mood as well as in his bodily symptoms. He is less afraid of the threat of disability and more independent.

METHOD OF APPROACH

There are 20 patients in the series reported here. Seven of these are children, aged between three and eleven years; the mean age is 7.1 years. The age range of the remainder is seventeen to thirty-nine years, and the mean age 29.0. There are 11 males and 9 females.

All the patients were first seen in the out-patient department of a general hospital, and most were investigated and treated as out-patients. Four patients (cases 14, 15, 18, 19) were admitted to a psychiatric clinic for some weeks.

In every case, the diagnosis of bronchial asthma was made by a general physician, and the patients were sent for psychiatric appraisal because it was felt that such an approach might be valuable. Hence this series is not a true sample of the asthma population as a whole, as the patients were selected on psychiatric grounds. There is no dispute, however, about the nature of the asthma itself, nor about its severity; some of the patients (for example, case 10) when they had severe attacks were very ill. I do not maintain that emotional tension is as important in every patient with asthma as it was in these. I shall try to show that when asthma does occur

as a reaction to stress it is worth while to aim at the relief of tension by every means at our command.

The period of time over which the patients were observed ranges from over three years to a few months; the mean is 19.9 months.

The method of investigation may be outlined briefly thus: The patient is encouraged to describe the circumstances of onset of his illness, what he was doing and how he was feeling at that time, whether his work was going well or ill and his domestic life contented or upset by bitterness, strife, or the qualms of conscience. When the onset is far back in childhood it may be difficult to reconstruct its setting, but even here the structure of the family may tell us much: the mother who is too possessive and too concerned about her child; the parents who are at loggerheads so that the child is a pawn in the struggle between them; the only child upon whom are centred all his family's hopes and fears. The history of the asthma is then surveyed, and the ebb and flow of its intensity related to the events of the patient's life. The situations in which attacks appear are closely examined. It will usually be found that these have a pattern.

Case 11. Myra was the only child of parents who both were anxious and rather prim. She was a girl of spirit, and in her youth yearned for romance and adventure. When she was eighteen, a Government office was set up in her home town, and she went to work there as a typist. She made many friends, and began to enjoy a richer life than she had hitherto known. She went to parties and dances and the theatre with friends of her own age, and savoured to the full these new joys. Her parents said nothing, but she began to feel the silent pressure of their disapproval bear upon her more and more heavily. After about a year the anxiety thus engendered erupted in a nervous breakdown, and this was quickly followed by asthma. For the next four years she had frequent attacks. These occurred, as a rule, when she was preparing to take part in some activity of which her parents disapproved, such as going to the opera. 'The asthma stopped my gay life for four years', she said. 'I wanted to go out, but couldn't.' In other words, the asthma had the function of preventing her from doing that which her conscience, and her father, condemned.

She struck up an acquaintance with a 'pen-friend' abroad, and as this ripened, her asthma dwindled and ceased. When the friend came home, she was married to him; they then decided to go to the Colonies. Myra knew that her mother would be disturbed by this decision, and as they travelled down in the train to tell her parents of it, she had an attack.

The pattern here is that of conflict between a natural independence and appetite for life and the need to obey parental wishes; the anxiety and guilt which sprang from this conflict precipitated asthmatic attacks.

RELATION OF THE ILLNESS TO STRESS

Children

In 6 of the 7 patients, the asthma made its first appearance at a time when the patient was the sole child in the family. Five of the six were only children, and the parents of the sixth (Brian) adopted another child when Brian was four, about two years after the onset of his asthma. In the seventh patient (Ellis) the first attack occurred after the birth of the next child. In short, the illness broke out either when all of the mother's care and concern were focused on the patient, or when they were being withdrawn from him to the next arrival.

The mothers of these children may be divided into two groups: the brisk, practical, business-like women who did not take kindly to the task of bringing up a young child (3, 4), and the anxious, troubled mothers who fussed over their children, or leaned on them too heavily for emotional support (1, 2, 5, 7). The two mothers in the first group often showed irritation and impatience with their offspring.

Case 3. Ellis's mother said: 'He nearly sent me up the wall at Christmas—he fidgets so. He worries a lot and that irritates me. He's really infuriating. His father loses patience, but I take it out on myself.' Her pent-up anger manifested itself in two bodily symptoms—headache and menorrhagia (O'Neill, 1952).

Attacks of asthma were brought on much more often by anxiety than anything else.

Case 4. Brian's parents, since they could not have any more children of their own, decided to adopt one, and when the new baby was brought into the house, Brian had five successive attacks of asthma. His mother said 'If I spend time with him alone, he's happy. He is thin-skinned and easily hurt. He had his two worst attacks when my mother was ill.'

In the youngest child in the series (Carol, aged 3) the state associated with attacks could best be described as tension. When he was free to do as he liked, in play therapy, he chose games of violence, such as flinging bean-bags against the wall. His mother was advised to allow him to let off steam, and lose his temper, without effort or restraint, and she reported that on this regime he had at least one 'paddy' a day, and no asthma. This little boy had a vast fund of nervous energy which needed outlet in violent muscular activity, yelling, and kicking; it seemed that if this were dammed back, he sooner or later had an attack of asthma.

One or two of the children were so anxious that almost any cause of emotional excitation could set off an attack.

Case 2. Peter's mother said 'He'll get it if he runs about, or gets excited, if he is going out to visit his aunts, or to a party, or if he is sad.'

Adults

In 5 of the 13 adults, asthma began under the age of five years. Two of these were only children, one an unwanted child, and in the other two the onset coincided with the advent of a baby brother.

The circumstances of onset in 2 of the remaining 8 were not clear; whilst in the other 6 the illness first appeared in the setting of an intense emotional experience.

Case 19. Harold, aged thirty-nine, was an only son, who was devoted to his mother. One evening, during the early part of the war, he was taking cover from the bombs in an air-raid shelter, when he suddenly recalled that his mother was alone in the house. He made to leave the shelter, but his companions held him back, saying that the blitz was very heavy and that he ought not to risk his life. After a tussle within himself he gave way and stayed in the shelter until next day, but an acute conflict continued in his mind between the drive for self-preservation and the urge to protect his mother. In the morning, he noticed his breathing to be harsh, and a little later he had an asthmatic attack.

The trigger for attacks, in all these patients, was the awakening of strong emotion, especially anxiety, resentment, and feelings of guilt. This third element, which showed itself as uneasiness, or an inexplicable dread, played

some part as a determinant of attacks in 8 patients, although it was not always so obvious as in the case just cited.

In two patients resentment was predominant.

Case 10. Mildred, when in health, was a cheerful, sharp-tongued, ribald Londoner who liked gaiety and talk; her husband was a silent, self-contained, rather morose man who never showed his feelings. This difference in temperament caused no trouble between them until Mildred had bronchitis in 1936; on the heels of this came the first attack of asthma. She had violent fits of coughing throughout the illness which usually passed over into tightness of the chest and asthma; the principal stimulant of these fits was anger with her husband: 'He won't talk; goes to sleep in his chair! This annoys me, and I get a tight feeling, or a fit of coughing.' 'I get that wild in fits of coughing. Once I flung the alarm clock downstairs.' There were other precipitants of asthmatic attacks, such as illness in her children, but resentment against her husband was the most important.

In the rest, anxiety from one source or another far outweighed other causes of attacks. Its sources were multifarious. One patient (15) felt acutely embarrassed by the knowledge that he was illegitimate; when he was able to bring himself to speak of this before other patients, in group therapy, he had great relief. Another (20) began after his discharge from the Forces to suffer a strong urge to expose himself to women; he fought daily with this impulse, and the mental distress thus aroused ushered in asthmatic attacks.

Case 17. Charles, aged twenty-five, worked in a publishing firm and took his work very seriously. When his superior went on holiday he took on an extra burden, became anxious about finishing his tasks in time, and had an attack of asthma. Another attack came when his wife was ill in hospital. He noticed that attacks would come on in the phase of remorse after a quarrel, or if he felt unsafe, for example, in a ship at sea on a rough crossing.

METHOD OF TREATMENT

The children were all treated as out-patients. The first principle of therapy is that mother and child are a unit, and both must be treated; the mother needs as much attention as the child, and perhaps even more. The aim of treatment of the mother is the modification of those morbid attitudes which contribute to the illness of the child, such as over-concern or the irritability which masks real anger. Direct interview was employed for the mother and older children, and play therapy for the younger children. The methods used have been described elsewhere (MacKeith and O'Neill, 1951).

Four of the adults were treated in a psychiatric clinic for a few weeks. Treatment was then continued in the out-patient department. Three of the four were much benefited by their stay in the clinic; their asthma improved considerably, and they remained better than they had been before. My impression was that if some of the other patients could have been given in-patient therapy, they too would have made a more secure recovery. To some extent, the results of psychological treatment of stress disorders depend upon the amount of time spent on the treatment. The fourth patient treated in the clinic did not improve at all. Although it was plain that her attacks were linked to ill-feeling towards her husband, she did not get any better with group and individual therapy, and left the clinic with her

asthma unchanged. Three years later she told me that she had been helped a great deal by a course of injections; with the improvement in the asthma, she had been better able to cope with her difficulties at home, and was not rendered so anxious or depressed by her husband's behaviour. It is clear that in this case we had concentrated too much upon the psychological determinants of the illness and neglected the physical. This was the only patient in the series in whose illness a physical determinant appeared to play an important part.

The treatment was adapted to the gravity of the illness. When the asthma was more or less continuous, distressing and disabling, frequent interviews, without long breaks, were given, with an attempt at fairly deep analysis of motive and feeling.

Case 9. Stella, aged thirty-six, first came to me when she had suffered from asthma for thirty-four years. She was an intelligent woman with some insight, who recognized that emotional tension was bound up with her attacks. In the search for the sources of tension, she laid blame on her attitude to work—she was self-critical, doubted her own capacity, and became agitated when she had to undertake any special duty. Her own view was that this anxiety was the major cause of attacks. Dream analysis soon showed, however, that at a deeper level she was preoccupied with her relationship with a man (Chris). Chris was already married, and during the course of treatment she had a long struggle in her mind to get free of her attachment to him; this she did in the end achieve. The dreams then took up the theme of her subservience to her mother, and this was also slowly worked out. In time she was able to admit to a strong desire to marry, and shook off the inhibitions which had beset her, took more part in social life, and expanded her literary and cultural interests. Severe asthmatic attacks ceased when she began treatment, and there have been none since. She had one spell of vasomotor rhinitis which lasted a few weeks.

When the asthma was not so severe, interviews could be more spaced out, and if all was going well could be discontinued, the patient being free to call on me again if he met with a disturbing situation with which he could not deal.

Case 18. Colin, aged twenty-four, began his treatment in a psychiatric clinic and was an in-patient for some six weeks. He took part in group therapy and the community activities of his ward, and showed himself to be an able, sensitive and thoughtful person. He accepted without difficulty the concept that his asthmatic attacks were associated with intense guilt-feelings, and his eczematous rash with frustration and resentment. He lived a long way from London, and could not attend often for interview, but after he left the clinic he went on thinking along the lines suggested to him, and observing his own reactions and symptoms. He wrote long reports to me about his observations, and his treatment was conducted, as it were, by correspondence. He continued to improve, and now—four years later—is free from asthma and has very little eczema.

PROCESS OF PSYCHOTHERAPY

The mechanisms contained in the process of psychotherapy may be outlined thus:—

(1) *Alteration in the patient's environment.*—When conditions at home, for example, were very disagreeable an effort was made to modify them by interviewing the patient's relatives, and making what adjustments were possible in material circumstances.

(2) *Reassurance and support.*—The patients were encouraged to discuss freely and frankly their problems and difficulties in the knowledge that they would be heard with sympathy and understanding, and without criticism. A relationship of friendship, trust and confidence between patient and physician is the ideal; it is inevitable that in every therapeutic relationship there will be phases in which the patient displays hostility towards the therapist, but he can be guided to comprehend the meaning of his feelings, and indeed to learn from them. Reliance on the physician must be handled wisely, and it should not become essential to the patient's well-being. His illness is not over until he is independent.

(3) *Restoration of equilibrium.*—The principal task in psychotherapy is to bring about harmony between the conflicting forces in the mind—the neutralizing of strong irrational doubts and fears, the ventilation of resentment, the dissipation of guilt-feelings. This task needs time; the more severe the disturbance, the more time is needed.

RESULTS OF TREATMENT

With the method of treatment outlined there were successes and failures, and much can be learned from both.

Children

Case 4. A year after Brian's first attendance, his mother told me that his attacks of asthma were but few and mild, and he was little troubled by them. His asthma was, then, improved although not fully recovered. The key to this improvement was the modification in his mother's attitude. Early in his treatment, she said: 'I've been irritable with Brian, and short-tempered; I regret this. I try to make it up to him.' I suggested that she should spend one period of every day alone with the child, and give her whole attention to him. She did so, and he became at once more cheerful and less tense. Brian's mother was alert, shrewd and eager to learn; she accepted the view I put to her of the pathogenesis of the boy's illness and acted upon it.

Case 9. Peter's mother was a timid, plaintive woman who admitted that she had been very nervous during her only pregnancy. Peter had eczema in infancy, and a good deal of other illness; his mother worried excessively about him, and he slept in her bed for a large part of his childhood. It was difficult to make any useful contact with this boy, as he was inarticulate and guarded in his manner. He made a very low score on intelligence tests, and although some of the poor performance might perhaps have been the outcome of anxiety, he was without doubt innately backward. His mother showed no enthusiasm for bringing him to the child guidance clinic, and broke off attendance after three months. Peter's asthma, so far as I know, is unchanged. Here, I had to contend with the serious obstacles of backwardness in the child and lack of adaptability in the mother, who could not, or would not, alter her intense possessiveness and 'smothering' of the boy.

Adults

Case 2. After nine to ten months of treatment, Stella remarked that she had not been so well for twenty years. This was very flattering, but I reminded her that no recovery could be complete until the patient was independent of both doctors and drugs, and could meet the hazards of life without undue emotional reaction. By this criterion, she has not fully recovered, but it is true that in spite of some uncomfortable happenings in her domestic life, she has been free from asthma for several months at a time; in the thirty odd years of her illness, such freedom has never occurred before. The key here is to be found in Stella's intelligence, sensibility, and desire to get well. Although she has lived as a chronic invalid all her life, her

spirit is not broken, and she still strives forward to a fuller life. The chief therapeutic tool was dream analysis. Because of her hunger for self-knowledge, I recommended to her the works of Karen Horney, and she read and re-read these avidly.

Case 11. Myra, when she came to see me, gave the story of her asthma very clearly, and seemed to be in no doubt that experiences which aroused anxiety were likely to set off asthmatic attacks. After her first few visits, she went abroad with her husband, and I did not see her again for about three years. Then in response to a follow-up letter she sent me a long account of the course of the illness over these years, well and neatly set out in typescript. Since she still had occasional attacks, her husband urged her to attend for psychological treatment. She agreed that as the asthma was emotional in origin this was the sensible thing to do, but nevertheless she felt very reluctant to begin, and resisted his advice for some time. When she did decide to attend, she had an attack on the eve of her first appointment. Her dreams contained many references to me, and the way in which I was depicted betrayed her resistance to therapy. She attended twice only, and then failed several appointments, making a number of excuses for her failure. Finally she wrote to me to say that she was not inclined to continue therapy just then, but might do so later. I concluded that her own inner resistance was so strong as to prevent her cooperating in treatment. This was a therapeutic failure, as I had not contrived to interpret the resistance to her in such a way as to help her to overcome it. One of the main roots of the resistance was her fear of insanity (there had been some mental illness in the family) but she could not see it as irrational, and in the end it overcame her.

TABLE 1
RESULTS IN 20 CASES

Children:	Much improved (no attacks)	2
	Improved	3
	Improved and relapsed (still under treatment)	1
	Unchanged	1 (Peter)
Adults:	Much improved (no attacks, or attacks few and slight)	7
	Improved (attacks fewer and less severe)	1
	Improved and relapsed	2
	Unchanged	3

Signs of good omen were high intelligence and capacity for change; signs of bad omen were a strong resistance to therapy and the presence of other stress disorders. For example, Muriel (case 13) had, in addition to her asthma, migraine (O'Neill *et al.*, 1952), various bodily pains, and anxiety attacks.

COMMENT

It seems fair to conclude, then, that in certain people asthma may appear as a reaction to stress, and that for some of these patients psychotherapy is useful.

The statement is sometimes heard that in such and such a case the asthma could not be psychogenic because it began in early childhood. This objection is groundless. Never again in the whole of life are emotions so intense, so overwhelming, as in childhood, when the personality is not yet well enough formed to exert some measure of control over its own reactions, and is swept away on a tide of feeling. It is not easy for the adult to recapture the vivid fears and terrors of the first years of life, or to project himself into the mind of the child who is ill.

As with the other stress disorders, many different remedies have been

proposed for asthma, and some successes have been reported with them all. It is difficult to escape the inference that there must be some thread running through them—perhaps the thread of faith: the conviction of the doctor and his patient that the remedy will work. It usually does work, at any rate for a time, but if the asthmatic attacks spring from emotional tensions in the personality, and these are not dealt with, the attacks will return.

Some of the patients had a resistance to the psychiatric approach to their illness, but this resistance was not, in the main, a serious problem. Two adult patients (8, 11) discontinued their treatment because they were alarmed at the prospect of facing up to the unpleasant things in their own minds. One child (Peter) did not attend the clinic because his mother was antagonistic to the notion of psychiatric treatment, and tried to deny that Peter was in need of it. Perhaps with more skill in the handling of resistance these failures might have been avoided.

None of these patients had any systematic physical treatment while they were under psychotherapy. Some used an inhaler if it was required, and indeed I made a practice of counting how often it was used; if psychotherapy was effective, the inhaler was seldom or never needed. Several patients did breathing exercises. It was my impression that the value of these was to some extent due to the factor of suggestion.

SUMMARY

The results of psychiatric investigation and treatment of 20 patients with asthma (13 adults and 7 children) are reported. The group is a selected one, being made up of patients referred for psychiatric appraisal.

The asthma first appeared, in the children, either when the patient was the sole child in the family or shortly after the birth of the next sibling. In most of the adult patients the onset of asthma coincided with an intense emotional experience. In both adults and children emotional tension—mainly anxiety, resentment and guilt—was by far the most important precipitant of attacks.

The results of psychiatric treatment were: Recovered or much improved, 9; improved, 4; improved and relapsed, 3; unchanged, 4. The reasons why treatment was effective in some cases and not in others are discussed.

I am indebted to my colleagues at Guy's, Charing Cross, King's College and University College Hospitals for sending me the patients under their care.

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ISONICOTINIC ACID HYDRAZIDE

FURTHER EXPERIENCES

By A HUMAN GUINEA-PIG.

In a previous article (*The Practitioner*, June 1952, p. 605) a man of sixty-one, with an old but progressive tuberculous lesion in the remnant of his left lung, told how he was rendered afebrile and returned to activity by taking isonicotinic acid hydrazide (isoniazid). The account covered the period of the first month's treatment, and this is a continuation of that account.

THE SECOND MONTH

At the beginning of the second month the dose of the drug, which was between 4 and 5 mg. for each kilogram of body weight, instead of being given four-hourly so as to maintain a constant concentration in the blood stream, was given in two doses at 9 a.m. and 9 p.m.; it seemed reasonable to suppose that the temporarily greater concentration might reach reserved areas where the mycobacterium was building up his forces for the next attack.

Half way through the second month the guinea-pig, not unmindful of the obligations of an experimental animal, lay in the sun in a clearing in the wood with few clothes on. It was pleasant and he went to sleep for two hours round about noon. He was sunburnt and subsequently did some extensive peeling. Normally, sunlight is an excitant to an active tuberculous lesion, although in graduated doses in fibroid cases I believe it to be beneficial. I have known it to be lethal in active early cases, and in a hot summer a number of cases of pulmonary tuberculosis of the exudative type in young people are activated or reactivated by over-sunbathing. Hope Gosse recorded 11 such cases in 1933.

The guinea-pig developed an evening temperature of 100° F. (37.8° C.), an increase of sputum, and a feeling of malaise, but not of tuberculous malaise. A normal active life was led and all the symptoms subsided in five days. Apparently one can take liberties under isoniazid.

CESSATION OF TREATMENT

At the end of two months the drug was stopped. The slight apprehensiveness previously mentioned, to which one had become habituated and had almost forgotten, was now noticeable by its going, as though one were free from discipline and home for the holidays, or had suddenly ceased to be overdrawn at the bank. There had never been any euphoria. I fancy that must be due to the patient's emergence from great toxicity, the result of comparative states: like the euphoria of one who goes to live in a slum after having been in Belsen.

As the action of isoniazid, so far as is known, is bactericidal only, and as the *M. tuberculosis* is not a rapid breeder, like the common cocci and vulgar viruses, it seemed silly to go on taking the drug after it had apparently done its job and thereby perhaps encourage those mutant forms that know how to deal with the stuff. They seem to be present in every *M. tuberculosis* army, even if the patient has never taken isoniazid. This probably means that at some time, possibly in preparasitic days, the mycobacterium has come across the isoniazid method of attack. Man himself owes much to his own mutability to adverse circumstance; bacteria with their keener strife and pressing generations must be much more readily mutant. It remains to be seen whether the isoniazid-resistant bacillus is a nicer or nastier parasite of man; there is evidence that the streptomycin-resistant form is definitely nastier. The ideal antituberculosis drug may well be one which does not eradicate it, but encourages mutant forms that are merely saprophytic.

About this time the report on the sputum at the end of the first month came in; it was negative to direct smear, but positive on culture; the cultured bacilli showed no resistance to isoniazid, PAS, or streptomycin. Later it was learnt that the sputum at the end of the second month was negative on culture.

RECURRENCE

Disappointingly, after three weeks of normal life, tuberculous activity again made itself felt: slight evening temperatures to 99.6° F. (37.5° C.), predawn moistnesses rather than sweats, aching of the knees, the not unpleasant languor, and all the mental symptoms known of old—the coloured, rather dramatic picture thinking, the metrical thinking in words—several sets of verses were written in this phase—a lessening of idea and concept thinking, and a return to more primitive modes of thought, smell, taste and touch thinking.

REMISSION

Not only was it disappointing, it was exasperating, because the grass in the guinea-pigs' four-acre orchard had to be cut at this time and piled to rot round the trees. He determined to do his hay-making—which consisted largely of raking, some carrying of large but light bundles of grass, and a certain amount of scythe work—under cover of isoniazid, which for the occasion was stepped up to 5 mg. per kg. After the first day he was very stiff, the muscles over his afflicted lung were sore, but the temperature was not increased above its previous slight febrility. That night he read a rather panicky leading article in the *Lancet* about vile variants of tubercle bacilli, resistant to isoniazid. Next morning at dawn therefore he shouldered his rake, not only under cover of isoniazid, but of the nauseating PAS also, which acted like a charm in clearing the pain in the muscles and stiffness. For a fortnight he followed that routine, up at 4.30 a.m., raking and scything until about nine when the hay became too dry to stack for rotting purposes, then a normal day and bed at 9.30 p.m. The evening temperature disappeared and there has been no febrile response to this exercise, which has

brought a wonderful feeling of fitness and freedom of the chest muscles. After a fortnight both drugs were stopped, but the early raking of dew-saturated hay continued. At the time of writing, three weeks after the cessation of drug taking, the guinea-pig is afebrile, feeling very fit, has about two ounces of sputum, all in the night—in fact is suffering from bronchiectasis rather than tuberculosis. His erythrocyte sedimentation rate is half what it was at the beginning of treatment—about 40—and seems to have stuck there.

DISCUSSION

The guinea-pig has thought on these things; *ab uno disce omnes*, and the following statement has the traditional dogmatism associated with that tag. Isoniazid kills the army of tubercle bacilli in the field. It cannot kill the source of this army, those lurking in calcareous fastnesses and caseous cities. Exercise, which increases the blood supply through the lungs from four litres a minute to thirty litres—or did when my old copy of Winton and Bayliss was published—may open some of these reserve areas for attack. To be logical the exercise should be taken when the concentration of isoniazid in the blood stream is highest—half to two hours after being swallowed, and there should have been a restriction of fluids. Why pour this valuable drug at the time it is wanted too soon down the drain of the kidneys? And why in Heaven's name use that uncertain drug tuberculin or calciferol 'to increase the vascularity of tuberculous areas by the use of an ancillary drug which will produce a focal reaction' (*The Practitioner*, July 1952, p. 86), when one can use exercise which can be safely graduated? I once saw the medical superintendent of a sanatorium kill several patients by giving them thyroid extract; he did not know it can be lethal in pulmonary tuberculosis. In the very rare cases in which exercise in some form is impossible it might, in minute tentative doses, be useful.

Rest has long been the chest physician's fundamental treatment because it is the only non-operative way in which he can lessen lung movement, the road of safety and the path of wisdom, the refuge from which the consumptive ventured at his peril; yet, when the blood stream carries a bactericide which we long to see getting at our foes, this rest may well be an outgrown creed, a barrier and a delusion. Besides, it is unthinking to worship a form of natural treatment which is by no means universal in application; chilblains, renal calculus, most forms of fibrositis and a host of atrophies are made worse or caused by rest, not to mention the senilities and atrophies that come from lethargies of mind.

The disappointing results of isoniazid in many sanatorium cases may well be due to the fact that the barrier of exudation, assisted by rest, keeps isoniazid from its victims. When isoniazid is triumphing or has triumphed over the tubercle bacilli's army in the field, it is obvious that the victory should be exploited. Eventually the patient's recovery will depend upon his

own resistance, and alternating exercise and rest, good food and fresh air, the ancient requisites of health, not the perquisites of cranks and invalids, these shall be its foundations. One of the primal truths that every general practitioner knows, but is often forgotten by those in high places, is that a musculature in being—like a fleet in being—is as another heart.

So far as this guinea-pig is concerned, if, as is likely, another tuberculous army masses to attack him, he will go against them with foot, horse and artillery—PAS, streptomycin and isoniazid—and he will give these every opportunity to manœuvre by exercise. Except that the danger of hæmoptysis is slightly increased, very slightly in a fibroid case like his, this is a logical procedure. A short, sharp course, lasting about a fortnight seems to be indicated. The reasoning for the long course after the toxic symptoms have gone seems to be fallacious and, like the continual spraying of trees, bad natural history.

The issue is in the hands of God, but unless the mammal uses his mind he shall perish.

POSTSCRIPT

The galley proofs afford an opportunity of sending the latest news of the front, which like the Korean front at the moment of writing is quiet, the balanced quietness of equally massed strengths. A wise commander in a lull tries to see his contest in perspective. In this case he sees his puny affair as a microscopic part of the great war between man and *M. tuberculosis*, a war which was old when Isaiah sang, which has been a major factor in shaping human destiny and time and again has diverted the course of human history. It is with this view in mind that a new anti-tuberculosis drug may be more important to *Homo sapiens*—over the centuries—than a world war.

To return to the trivial, to this guinea-pig: at the moment of writing he is not suffering from the attacks of *M. tuberculosis*; he knows that, because he is not feeling the particular form of regression which is the characteristic answer to it and of which the sovereign mind gives the first hint. So far as he is suffering at all, it is from a secondary infection, as evidenced by an ounce or two of purulent sputum, that is to say, from a rabble which contains even older enemies of man than *M. tuberculosis*, who like wasps with a plum are ever ready to exploit a breach in the frontiers. After his anaphylactic shock with penicillin, the severest physical experience he has ever had—he is a little shy about seeking help from the poisons of the moulds against them. There are other methods. We must take thought.

C G.L.

THE TREATMENT OF ECZEMATOUS DERMATITIS

By H. R. VICKERS, M.B., M.Sc., F.R.C.P.

Consultant Dermatologist, Rupert Hallam Department of Dermatology, Royal Infirmary, Sheffield.

THIS short article is written to try and answer the following query sent to this Journal recently:—

'I will be obliged if you will endeavour to clear up the confusion in my mind regarding the treatment of eczematous dermatitis. I have tried all the treatments recommended by the hospital skin departments, and all the textbook treatments. The condition still remains a nightmare to me as I appear to see so many cases and never get a satisfactory result. Several of my patients after being seen at hospitals and seen privately by consultants have tried other remedies in desperation and in nearly all the cases the "quack" treatment has succeeded in a period of weeks where the orthodox treatment has failed for months and sometimes years. The basis of these treatments appears to be molasses or some white ointment prescribed by people who dabble in homœopathic medicine. There is no use closing our eyes to the fact that the "quack" treatments are a success in a greater proportion of cases just as the orthodox treatments are a failure in the greater proportion of cases'.

This question raises one of the most difficult problems in dermatology and it also demonstrates well the disadvantage the dermatologist has compared with the general physician. The patient with any skin disease expects, and often demands, complete cure, whereas with internal diseases, provided the cough is not too troublesome and the epigastric pain not too frequent, the chronic bronchitic and dyspeptic is quite happy. In disease of the skin, the patient can see his pathology too well and examines himself minutely for the smallest evidence of either recurrence or extension of his condition. The old gibe that the dermatologist never cures his patient is true only in so far, for example, as the chest physician never cures his chronic bronchitic nor the gastro-enterologist his dyspeptic.

THE VARYING TYPES OF ECZEMATOUS DERMATITIS

The difficulties of treating chronic eczematoid dermatitis are essentially due to lack of knowledge of the mechanism underlying the process. It is probable that in this condition the epidermal cells have become specifically sensitized to some allergen which may reach the epidermis either from without or from within the body. Histologically, all types of dermatitis, whether produced by contact with either primary irritants or with specific sensitizing agents, are indistinguishable from cases of so-called eczema. If the various gradations of dermatitis are considered these throw some light on the probable nature of eczema. This consideration can only be brief in an article of this nature.

The first type is dermatitis due to contact with a primary irritant, and is produced in any average person who comes into contact with some noxious agent: common examples are the dermatitis of the hands produced in washerwomen by repeated exposure to alkaline solutions; dermatitis of the lower leg in coal miners from the irritation of sweat and dust; dermatitis of the forearms and neck in cement workers, and so on. The next type is sensitization or 'contact' dermatitis which is produced by contact with some agent only after the skin has been specifically sensitized to that substance. As I have stated in a previous article in *The Practitioner* (1950, **164**, 226), the establishment of such sensitization depends upon the length of exposure to the substance, the age of the patient, the emotional state, and perhaps on some idiosyncrasy of the patient whereby he is more easily made sensitive to substances; common examples of this are dermatitis caused by suspender buckles, spectacle frames, cosmetics, hair dyes, plants, and local applications such as the sulphonamide drugs and flavine.

The next stage in the story is shown by *secondary sensitization dermatitis*. When an area of sensitization dermatitis has been established, if the allergen is still coming into contact with the lesion, as for example a suspender buckle on to an area of suspender dermatitis, sooner or later areas of dermatitis appear on other parts of the body not necessarily in contact with the allergen. An obvious explanation is that since when one area of skin is sensitized to a substance the whole of the epidermis is also sensitive to that substance, it is reasonable to assume that a minute amount of the allergen is absorbed through the primary sensitizing area and comes into contact with other parts of the skin through the blood stream, thereby giving rise to the secondary areas of dermatitis. These secondary areas are analogous to eczema, which is the next stage in the story. If the patient whose skin has been sensitized by the local application of a sulphonamide preparation takes at some time that preparation by mouth, a generalized sensitization dermatitis will occur due to the sulphonamide radicle coming into contact through the blood stream with the sensitized epidermis. Thus ingested substances are able to produce an eczematous reaction.

In susceptible or 'eczema prone' individuals it is not unreasonable to postulate that their epidermis may become sensitive to many different allergens, either taken by mouth or produced in the course of metabolism, and this may be the underlying mechanism in these cases of eczematous dermatitis in which there is no obvious external cause. As with the establishment of sensitization dermatitis, age (particularly with regard to hormonal activity) and emotional stresses play a part in the course of eczematous dermatitis, and these must be considered in treatment.

TREATMENT

The first essential is to search for a possible cause. Not infrequently patients complain of eczematous areas on the forearms which are primarily due to

longstanding contact dermatitis of some other parts of the body. This is often not mentioned in the history and is found only after direct questioning and complete examination. The cause of primary sensitization contact dermatitis can be ascertained by careful history taking, paying particular attention to the site of onset, which must be correlated with likely substances coming into contact with that area. Any substances which are suspect are used for patch testing, and the more carefully the history is taken and the more substances tried in the patch test, the fewer the cases of eczema in which an external contact cause is not found. If a cause is found, avoiding contact with the substance is the only certain cure.

There still remains a group of puzzling cases presenting usually as well-defined areas of eczema with erythema, vesiculation, weeping and crusting of the skin, and these must be treated empirically.

Local treatment.—In the acute cases in which there is itching, erythema and weeping, wet dressings of a shake lotion should be used. The lotion is applied to the area soaked in at least four thicknesses of surgical gauze or old linen, which is changed so frequently that the dressing never becomes dry. The secret of success in this stage depends upon the wet dressings being kept wet. Calamine lotion, or a lotion, which I prefer, consisting of

Fuller's earth	1 ounce (31 g.)
Zinc oxide	1 ounce (31 g.)
Glycerin	½ ounce (14 g.)
Water	to 12 ounces (342 ml.)

is extremely useful.

Since these acute areas have lost their waterproof horny cover, they should not be washed with soap and water; the alkali of the soap removes the forming epithelium and the water is absorbed into the exposed cells by osmotic pressure. Debris can be removed either by sponging gently with the shake lotion, with liquid paraffin, or with 1 per cent. 'cetavlon' solution.

If the area is secondarily infected, shake lotions cause crusting and are better avoided. In such cases, wet dressings of 0.5 per cent. silver nitrate solution (warning the patients that the clear solution will stain everything indelibly black); boric acid lotion; eusol lotion; 1 per cent. solution of brilliant green, and if the organism is penicillin- or chloramphenicol-sensitive, lotions of these antibiotics can be used.

As the activity diminishes, tar, either as 5 per cent. solution of coal tar or 0.25 per cent. crude coal tar, can be incorporated in the shake lotion. Later, calamine liniment or Lassar's paste can be used. The paste is applied either directly on to the area or on old linen; the area can be cleaned before application with liquid paraffin. Because of the solid matter it contains, Lassar's paste can be used even when there is a certain amount of exudation —the serum is absorbed by the solid particles. Often the patient is cured by these measures, but in resistant cases, crude coal tar, of strength 0.25 to 2 per cent., can be incorporated in the paste.

In more resistant cases, strong ointments may be tried. Each dermatologist has his favourite prescription; mine is:—

Yellow mercuric oxide	1 part
Crude coal tar	2 parts
Lanolin Petroleum jelly	āā 10 parts

And after using silver nitrate solution, I often find ointment of mercury, lead and zinc useful to clear up the condition.

In very resistant cases, occlusive dressing with a 'viscopaste' or 'coltapaste' bandage (Smith and Nephew) applied for seven to fourteen days is often effective, and if the legs are affected, supporting bandages to control venous stasis must be used. With all local applications, constant watch must be kept for any aggravation of the condition by the preparations tried.

Of other methods of local treatment, superficial radiotherapy is valuable, but this must be administered only by an expert.

General measures

(1) Rest in bed is necessary in extensive cases.

(2) Sedatives, particularly the barbiturates, should be given in adequate dosage. They help to relieve both the tendency to scratch and any emotional tension.

(3) Antihistamines seem to help some cases, but this is probably as a result of the sedative action and is not directly due to any antihistaminic effect.

(4) Non-specific protein shock produced by intravenous injection of T.A.B. vaccine at intervals of five days is sometimes effective.

(5) If there is any emotional upset, this when possible should be helped, since in many of these cases some nervous tension due to lack of adjustment either at home or at work seems to be responsible for the chronicity of the condition.

CONCLUSION

In this brief summary of eczematous dermatitis, I have tried to give an explanation of the processes involved so that the questioner's problems can be approached fundamentally. The fact that many patients do respond to patent remedies is due I believe to several factors. Many effective remedies for skin diseases are also potent epidermal sensitizers and as such are avoided by dermatologists. The subconscious reasoning may be that if a patient tries something himself and makes his condition worse, he is quite happy to accept responsibility, but the expert cannot as a rule take any risk with these preparations. Also the dermatologist only sees the failures of these patent remedies; obviously the cures are never referred to him, and so he perhaps loses a sense of proportion in their usefulness.

The third potent factor is the presence or absence of faith in the cure.

GENERAL PRACTITIONERS' FORUM

SOME INCIPIENT SYMPTOMS OF HEART FAILURE

By W. N. LEAK, M.D.

I WAS interested to note that in his excellent article on the clinical assessment of cardiac efficiency (*The Practitioner*, July 1952, p. 5) Dr. Paul White omitted to mention—as indeed most, if not all, textbooks do—one of the simplest and most significant signs of incipient cardiac failure in an ambulatory patient.

NOCTURIA

It depends upon the fact that in the early stages of myocardial insufficiency there develops during the day a subclinical œdema. The heart, as it were, economizes by reducing renal excretion. Then, during the night, when other calls on the circulation are diminished, the kidneys function more actively and the retained fluid is excreted. As a result the patient has to get up at night once or twice to empty the bladder. In this way inquiry into bladder function at night is one of the easiest, and with care one of the surest, ways of determining cardiac efficiency. This nocturia can, of course, easily be mistaken for that of an enlarged prostate but, quite apart from a rectal examination, the history will make the distinction clear. Typically, micturition is infrequent during the day and more frequent at night. Actually any getting up at night to pass urine should be looked on with suspicion unless there is obvious imbibition to explain it. Also the urine voided during the day is higher coloured and of higher specific gravity than that voided at night. All these points differentiate it from pure prostatic obstruction.

Having once made the observation on a patient, the next thing is to try the effect of digitalis. If the patient finds that digitalis diminishes the number of times he has to get up at night the diagnosis of incipient cardiac failure is confirmed, whatever its exact cause may be. Furthermore, this gives the patient a most sensitive guide whereby to control his activity. If he finds that he is having to get up more often (or even once) at night he is obviously doing rather more than he ought to do, or alternatively, if he is taking digitalis, the dose may need to be increased. Variations occur, of course, but the basic principle is simple and sound, and by intelligent use of this observation cardiac failure may be diagnosed in its very earliest stages; and, no less important, the patient can keep within his cardiac tolerance without any careful medical supervision. His working life will be prolonged and his nights made more comfortable.

With women the same thing holds, but women are so much more liable to get frank swelling of the ankles at night, from prolonged standing, varicose veins, endocrine dysfunctions, and the like, that the picture is not

so clear as with men; but even in such cases one or two grains of digitalis or its equivalent, taken every day will often greatly diminish their need to get up at night to pass urine, showing that the heart has not been functioning quite as well as it could and should, i.e., that a mild cardiac insufficiency is present which is often improved by iron and vitamin B complex, although this latter probably acts on the kidneys as well.

SWELLING OF THE ANKLES IN YOUNG WOMEN

In parenthesis, it is perhaps worth mentioning that there is a quite well recognized swelling of the ankles in young females which causes them much embarrassment and varies to some extent with the menstrual cycle. So far as I know the cause is unknown.

One severe case of mine has cleared up remarkably with 'priscol' which the patient has been taking for over a year. One other case also improved with 'priscol', but she seems to have been cured by marriage—which is not always the case! So 'priscol' seems worth trying in these unfortunate cases, for neither hormones, diuretics nor physiotherapy does them any good.

ANOTHER SYMPTOM IN WOMEN

There is another symptom in women which raises several interesting points, although it is less in evidence now with changed hair styles and housing conditions. This is that many women feel increasing fatigue when raising their hands above their heads, as in doing their hair or dusting high shelves. Although there may be several reasons for this, myocardial weakness is one of them, and it may be a very early symptom. When well marked it may even make ordinary dressing inconvenient or exhausting. I believe that there is an anatomical reason for this, for I have several times noticed, in men who have lifted up their shirts for the more cursory auscultation that may be all we have time for in busy surgery times, that various murmurs may be heard (usually systolic and in the aortic area) which disappear as soon as the arms are dropped to the sides. From this I infer that raising the shoulders and arms causes a drag on the great vessels in the thorax, which may well send up the intracardiac pressure. If this is so it would explain why this complaint of fatigue on raising the arms is so much more common in women than in men, for with the more sloping shoulders of women, compared with the squarer ones of men, lifting the arms must lift the shoulder girdle relatively more and so cause greater distortion. It would also fit in with the observation that not a few cases of sudden death in women are associated with stretching up to reach something from a high shelf. Here, presumably, the intracardiac pressure has been suddenly raised through stretching or torsion of the vessels and collapse has been the result.

A CAUSE OF SUDDEN DEATH

In connexion with sudden death it is noteworthy how many of these occur in the lavatory. I well remember Dr. (later Sir) Humphry Rolleston mentioning this nearly forty years ago, and in his opinion it was difficult to

decide whether death was due to straining or whether impending dissolution was not associated with the desire to go to stool. It ill behoves the clinical clerk of so great a master to be dogmatic where he expressed doubt, but it is at least a practical point that the prevention of constipation is most desirable in those with failing hearts.

THE RÔLE OF DEFÆCATION IN THE PRODUCTION OF PILES

By A. S. WOOLSTONE, M.R.C.S., L.R.C.P.

It is obvious that the function of the rectum and anus is to discharge fæces and not to expel its own loosely attached mucous membrane with its closely associated veins, thus producing piles, which are such a common complaint among civilized people.

In order to understand the etiology of this widespread complaint it is necessary to review the anatomy of the rectum and anus, together with the mechanism of defæcation. In its course from the middle of the third piece of the sacrum to the tip of the coccyx, the rectum describes three lateral curves; at its termination it bends sharply downwards and backwards into the anal canal. At this flexure the rectum is encircled by the attached fibres of the levator ani muscle. For far too long the levator ani has been primarily described for the part it plays in forming the bulk of the pelvic floor, whereas its action, suggested by its name—elevator of the anus—has been neglected. It is when the hitherto empty rectum is filled by peristaltically propelled fæces, that the desire to defæcate is felt, and then only after peristalsis has rammed packed fæces against the resistant, voluntarily controlled annular musculature of the anal sphincter.

Observation of defæcation in animals demonstrates first the drawing in of the anus followed by its dilatation with expulsion of the fæces; suggesting that what has happened is that the levator ani has pulled up the lower end of the rectum over the mass of fæces like a sleeve. The human being, in a crouched position on the lavatory seat, must use increased abdominal pressure to expel the fæces downwards against the upward thrust of the seat; this prevents the efficient elevating action of the levator ani, which is dragged downwards with the expelled fæces instead of being drawn upwards over it. The loosely attached mucous lining of the lower end of the rectum is thus encouraged to prolapse, carrying with it, and obstructing, the associated veins of the hæmorrhoidal plexus, and eventually producing hæmorrhoids.

From what has been stated it appears possible that correct drill at stool may have a part to play in the prevention of hæmorrhoids and in their treatment. Posture is important, the bolt upright position should be adopted with the lower end of the thighs taking the weight of the body, slightly lifting the buttocks off the seat, thus preventing the seat from being used as

counterpressure against the contracting abdominal muscles. The action of defæcation should be accompanied by drawing up of the anus in order to assist the levator ani to slip upwards over the fæcal mass. As a step further it might be suggested that drawing-in the anus could be used as a method of exercising a weakened levator ani.

MINOR SURGERY IN GENERAL PRACTICE

By W. RADCLIFFE, M.B., B.Chir.

All too often in the last few years have we heard the complaint that the general practitioner is in danger of becoming a mere sign-post to an ever increasing number of special departments in hospital. If this should ever happen it would indeed be a waste of time to bother him with a medical training, for such direction would be within the competence of an alert clerk or secretary.

If there is any truth in this criticism, surely some of the fault lies with those practitioners who, either because of apathy or because they have too large a list of patients to find time for it, have given up doing their own minor surgery, for which their training should have prepared them. Instead, they send all this work to the nearest hospital, where it is undertaken by the junior house surgeon, whose experience may be very limited. The general practitioner who does his own minor surgery will today reap no financial reward for it, but he will have the satisfaction of the good craftsman in work well done, and the gratitude of his patients who have been spared a time-consuming visit to hospital, and in whose eyes his prestige will be increased by his competence.

CHOICE OF TIME

The first essential for doing minor surgery is to make the time for it outside the usual surgery hours, with the possible exception of emergencies. Even in such cases, few emergencies, except perhaps burns and hæmorrhages, cannot wait an hour or so until the busy surgery has emptied, and the work can then be done without that haste which is fostered by the knowledge that there are others waiting to be seen. It is often an advantage to inject a local anæsthetic when the patient is first seen, and then to ask him or her to wait, during which period the analgesia will become more complete, and the doctor will have time to assemble and sterilize his instruments. I like to set aside part of a Sunday morning during a week-end on rota duty for cold surgery, such as the removal of sebaceous cysts, or circumcisions.

INSTRUMENTS REQUIRED

Every doctor will in the course of time develop a preference for certain instruments, and in my own case I like to use the smallest possible ones which will do the work, for this leads to neatness and delicacy of touch.

For example, Terrier's ophthalmic artery forceps, only three-and-a-half inches long, are more convenient than the conventional five-inch Spencer Wells, and a small-toothed iris forceps is very handy for neat suture work instead of the usual thick-ended dissecting forceps. For facial wounds I use the smallest nylon on atraumatic eyeless needles, which is expensive but well worth the extra cost, and I was fortunate in learning the use of Gillies' needle-holder from Sir Harold himself. Being single-handed I have found that a Kilner's spring retractor, which is self-holding, is useful when dissecting cysts or exploring small wounds, and small Kocher's artery forceps make the best tissue forceps. For local anæsthesia, when only a small amount is desired, a dental cartridge syringe is handy, and is always used before suturing cuts, the solution being injected generously into the sides of the wound under the skin surface, so that any overflow adds to the surface analgesia.

SUITABLE CASES

I now come to the type of minor operation which can be done in the surgery, but which is often sent to the hospital casualty department.

One of the most satisfactory of these minor operations is that of evacuating a *thrombosed external pile*. This is an ideal example for the use of local anæsthesia, which can be injected when the patient is first examined and the lesion diagnosed. He is then asked to wait until the end of surgery. If he is nervous, or if the analgesia is not quite complete, I reinforce it with gas and air or trilene analgesia, from a Minnitt or Cyprane apparatus. The relief after the clot is removed is instantaneous, and the patient is always highly gratified. The best dressing is a large sanitary towel.

Another simple operation, which I mention because it is not so well known, is the opening of a *subungual hæmatoma*. This is common in my practice because of the neighbouring shipyards. A small hole is burnt through the nail just distal to the lunula, using a small piece of red-hot wire. It looks terrifying to the patient, but is actually quite painless, as the nail is insensitive. It is far less painful than drilling or scraping a hole in the nail, which requires considerable pressure, however carefully it is done. Moreover, the hole shows no tendency to close. A piece of 'elastoplast' dressing strip covers the hole and exerts gentle compression to keep the nail down.

When local anæsthesia cannot be used, as in the presence of infection, trilene analgesia is quite successful, e.g., in opening *small abscesses* or *boils* or *septic fingers*. I have only described two examples of minor surgery, but the possibilities are, of course, legion. The last twenty-four hours brought to my surgery two foreign bodies in eyes, one cut forehead to be sutured, one splinter under the finger nail, one case of varicose veins for injection treatment, and one sebaceous cyst of the scalp. I never attempt the removal of a foreign body unless it is clearly visible, as nothing is more unsatisfactory than a fruitless search, when x-ray examination would have located it easily; and I never attempt more than elementary first aid for a fracture, for today even the simplest fracture work without x-ray guidance is courting disaster.

CURRENT THERAPEUTICS

LVII.—ERGOT AND ITS DERIVATIVES IN CLINICAL PRACTICE

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ERGOT is a fungus growing on the grain of cereals, and the official preparation is obtained from rye. The fungus goes through several stages of development and the resting stage (sclerotium) constitutes the drug.

CHEMISTRY

Ergot contains a large number of pharmacologically active substances, including a number of alkaloids. The active alkaloids are lævo-rotatory, and ergot also contains dextro-rotatory isomers of these which are inactive. The active alkaloids of ergot are all derivatives of lysergic acid and can be divided into two groups.

The important constituent of the first group is ergometrine, which is a combination of lysergic acid with *d*-aminopropanol. It is a water-soluble substance and is therefore well and rapidly absorbed when given orally.

The second group contains a number of rather more complex substances which are condensation products of lysergic acid with 2 to 4 molecules of amino-acids arranged in a kind of polypeptide chain. The most important constituents of this group are ergotamine and ergotoxine, which are closely related chemically and practically indistinguishable pharmacologically. These substances are insoluble in water and are therefore unreliably absorbed when given orally. Aqueous extracts of ergot contain little of these substances.

In addition, a number of derivatives of the ergot alkaloids have been made chemically, and some of them have proved of therapeutic interest. The most important are dihydroergotamine and methylergometrine.

PHARMACOLOGICAL ACTION

The ergot alkaloids exert three main pharmacological effects, namely:—

(1) Contraction of smooth muscle, including the uterus and the blood vessels. The stimulant effect is exerted directly on the smooth muscle and not through a nervous mechanism.

(2) Antagonism of the action of adrenaline, and paralysis of adrenergic nerves. Motor effects are prevented much more easily than inhibitory effects, but large doses also paralyse inhibitory receptors such as those in the intestine. These effects are produced by ergocoxine and ergotamine, and not by ergometrine.

(3) Stimulation of the sympathetic system by action on the central nervous system, causing sham rage. This effect is produced by ergometrine, as well as by ergotoxine and ergotamine. The action of the latter two drugs is rapidly counteracted by their effect on adrenergic nerve endings as described in (2).

ACTION ON THE UTERUS

For centuries, ergot has been used for its action on the uterus, and long before the nature of its active constituent was known. For many years it was believed that ergotoxine and ergotamine were the active substances, but the observations of Chassar Moir first suggested that another substance, more rapidly absorbed from the intestine, was involved, and this led to the isolation of ergometrine, the most important of the ergot alkaloids.

Ergometrine maleate can be given orally, intramuscularly and intravenously. It produces a powerful contraction of the uterus at and immediately after parturition, tends to hasten normal delivery, and after delivery hastens and sustains the normal retraction of the uterus, thus checking post-partum hæmorrhage.

The liquid extract of ergot (B.P.) produces its rapid effect on the uterus by virtue of its ergometrine content and can be used unless a very rapid effect is desired. Its one defect is its very unpleasant taste.

Methylergometrine (at present obtainable as 'methergine'—Sandoz), and which was synthesized by Stoll and Hofmann, is a synthetic derivative of ergometrine and is *d*-lysergic-*dl*-hydroxybutylamide-2. It has been claimed that it compares favourably with ergometrine for its oxytocic action on the human uterus, and that it is about one-and-a-half times as active as ergometrine.

Ergotamine and ergotoxine also produce contraction of the uterus, but the effect is slower even when given by injection and is not so reliable and satisfactory clinically. These substances are rarely used for their action on the uterus.

Dihydroergotamine was also synthesized by Stoll and Hofmann, in 1943. The hydrogenation markedly changes its pharmacological properties. It has a very low toxicity and is highly potent in antagonizing the action of adrenaline; its action on the blood pressure is slight. Its use in obstetrics and in the treatment of migraine will be discussed later.

ACTION ON THE BLOOD PRESSURE

Ergotamine and ergotoxine produce contraction of smooth muscle, including

that of the arteries, and this tends to raise the blood pressure. The effect of ergometrine in this way is only slight.

ERGOTISM

When ergot is taken over a long period it tends to produce chronic poisoning. Two forms of such poisoning have occurred: convulsive ergotism due to changes in the central nervous system, and gangrenous ergotism due to changes in the arterioles.

Gangrenous ergotism is seen in man and in many animals. It is due to ergotamine and ergotoxine, and has followed the therapeutic use of ergot. It is due to a powerful contraction of the smooth muscle of the arterioles; there is endothelial injury, obliterative arteritis and thrombosis. Effects are seen particularly in the extremities and in the intestine. The fingers, toes or an entire limb may slough off. In the intestine, ulcers are produced which involve particularly the lymph follicles.

CLINICAL USES

Liquid extract of ergot (B.P.), ergometrine maleate (B.P.), methylergometrine and dihydroergotamine are used in obstetrics and gynæcology. Except for dihydroergotamine they are used for their oxytocic action on the uterus. Ergotamine tartrate (B.P.) and dihydroergotamine are used in the treatment of migraine.

USE IN GYNÆCOLOGY

Certain patients suffering from *menorrhagia* of a minor degree are suitable for treatment with ergot or its oxytocic alkaloids. Women with small uterine fibroids who are approaching the menopause fall into this category, as do women with slightly excessive menstrual periods due to a temporary upset in endocrine function, which often occurs at the time of the menopause but may occur at any age. Large fibroids, pyosalpinx and endometriosis are the causes of menorrhagia too excessive to respond to treatment with drugs, and these lesions must be excluded. There remains a group of women without gross physical signs in the pelvis who find that an increase in the menstrual period is an inconvenience, but who are not becoming severely anæmic through loss of blood. They can be treated with liquid extract of ergot (B.P.), 2.5 ml., thrice daily by the mouth for three days at the menstrual period, or with tablets of ergometrine maleate (B.P.), 0.5 mg., thrice daily for three days at the menstrual period. Anæmia should be corrected by the use of iron.

Inevitable and *incomplete abortions* are treated by intramuscular injection of ergometrine, 0.5 mg., except in the case of severe bleeding. Any undue delay in the expulsion of the uterine contents should be treated by operative evacuation. Particularly suitable for treatment with oxytocics are *septic abortions*, not under chemotherapeutic control, when operation may be

inadvisable. Uterine hæmorrhage following abortion or operative evacuation of the uterus can be controlled with injections of ergometrine. For a rapid effect, ergometrine can be given intravenously.

USE IN OBSTETRICS

Ergot has been used for centuries to *control bleeding from the uterus* after delivery of the placenta but, since its isolation in 1935, ergometrine has replaced crude ergot and its alkaloids, ergotamine and ergotoxine. A more rapid effect than can be obtained with the drug given orally is usually required, so that the intramuscular route is chosen. Ergometrine maleate (B.P.) is given in doses of 0.5 mg., and can be repeated two or three times if necessary. It is used after vaginal deliveries and at Cæsarean section.

Whilst the uterine hæmorrhage which follows delivery of the complete placenta can be controlled by oxytocic drugs such as ergometrine and posterior pituitary extract, the problem of post-partum hæmorrhage during the third stage of labour has not yet been solved.

During the last few years ergometrine has been given deliberately before delivery of the placenta in an effort to *hasten the third stage of labour* and thereby minimize the loss of blood. Several different techniques are being tried. Ergometrine, in doses of 0.25 mg., 0.5 mg., and 1.0 mg., is given intramuscularly and intravenously. The experiment is being conducted in normal and abnormal deliveries, with and without the addition of anæsthesia. The timing of the injection varies. Ergometrine is given at the time of crowning of the head, at the moment when the anterior shoulder of the fœtus escapes from under the symphysis pubis, as the fœtal trunk is escaping from the vulva, and soon after delivery of the baby. Each particular technique has its advocates, who claim that the placenta is delivered very quickly after the birth of the baby, that blood loss is considerably reduced, and that the incidence of post-partum hæmorrhage is very small. Unfortunately, in a few cases the uterus contracts irregularly and a contraction ring forms below the placenta. The placenta becomes retained and has to be removed manually. In addition, the experimental use of ergometrine in the third stage of labour is being tried out, for the most part by expert obstetricians who advise early expression of the placenta by uterine compression and cord traction, if the placenta is not spontaneously delivered in a very short time. The method is not therefore universally applicable to midwives and practitioners engaged in domiciliary midwifery. It should be reserved for the use of obstetricians dealing with abnormal cases in hospital. The technique is especially useful for forceps deliveries under anæsthesia or for other cases in which post-partum hæmorrhage is likely to occur.

A different problem is that of the midwife or practitioner who, in the patient's home, is faced with a case of post-partum hæmorrhage which does not respond to ordinary measures such as Credé's expression of the placenta. Here the injection of ergometrine may be life-saving. Hæmorrhage is

stopped for the time being, time is gained to obtain help from the flying squad, and the patient can be admitted to hospital where the removal of the placenta must be undertaken.

Ergometrine is given by mouth, 0.5 mg. thrice daily for three days, in cases of *puerperal subinvolution*.

Lately, a synthetic derivative of ergometrine, methylergometrine, has been tried in place of ergometrine. It is stronger than ergometrine. Doses of 0.2 mg. are given intramuscularly or intravenously. The drug compares favourably with ergometrine in its effect on the uterus. It has the advantage of being tolerated in higher dosage, and it is cheaper.

A new semi-synthetic drug, dihydroergotamine, is supposed to act in cases of colicky uterine inertia by relaxing cervical spasm. It has no oxytocic action on the uterus. These claims have yet to be proven.

CONTRAINDICATIONS

Ergometrine and methylergometrine have been used in an attempt to induce labour. They are not particularly effective. The intensity of their action on the pregnant uterus is a variable one. Occasionally a prolonged spasm of the uterus occurs and the life of the fœtus becomes endangered. For this reason the drugs should never be used to induce labour. Similarly their use in attempts to stimulate the uterus in cases of inertia is contraindicated because of danger to the fœtus.

USE IN MIGRAINE

Migraine is probably caused by intracranial vascular changes, although the exact mechanism of its causation is by no means clear. It seems likely that the aura is caused by constriction of cerebral arteries, whilst the headache is due to dilatation and distention of cranial arteries.

Ergotamine tartrate has been used extensively in the treatment of migraine and beneficial effects are obtained, particularly when the drug is injected (0.25 mg.). Good results have also been reported with a combination of 1 mg. ergotamine tartrate and 100 mg. of caffeine, both given orally.

Dihydroergotamine is also effective and is less likely to produce undesirable side-effects such as pains in the limbs and abdomen, nausea and vomiting, which may be encountered with ergotamine tartrate. Dihydroergotamine can also be used safely during pregnancy without risk of producing abortion, and during menstrual periods without causing colicky dysmenorrhœa.

According to Professor D. M. Dunlop of Edinburgh (personal communication to the authors), *ergometrine* is highly effective in the treatment of migraine and should be considered the drug of choice among the ergot alkaloids.

Ergot alkaloids have also been used in a number of other conditions, but there is no clear evidence that they are of value.

REVISION CORNER

BLEEDING GUMS

BLEEDING from the gums is a symptom experienced by most people at some time or other. Many correctly attribute the bleeding to injury caused by a new toothbrush and no further steps are taken. Those who seek advice may pay a visit to their dentist, whilst many prefer a free consultation with their general practitioner. A few such cases fall strictly within the province of the doctor; many require dental care. Cogent reasons should be given for the need for an immediate visit to the dentist lest the patient procrastinate. It is desirable therefore to be acquainted with the diagnosis, the complications, and the treatment of the complaint.

The diagnosis of bleeding gums falls into two main categories. First, the local causes, which are responsible for the vast majority of cases. Secondly, the systemic diseases, in most of which there is a generalized tendency to bleed. In some instances systemic factors influence the progress of the local disease. In each case, the immediate cause of the bleeding is often the toothbrush.

THE LOCAL CAUSES OF BLEEDING GUMS

Trauma.—Hard toothbrushes are in popular demand in the belief that the teeth are cleaned more efficiently by them than by the medium or softer types of brush. This idea is no more logical than the suggestion that a wire brush would be best for cleaning the nails. Soft tissues are brushed with the hard ones and, in the mouth, the relatively delicate epithelium is damaged. The superficial injury caused by a toothbrush or toothpick causes momentary bleeding when the gums are healthy. In pathological states, bleeding occurs more readily and continues for a longer time. More severe trauma, such as dental extraction, may give rise to remarkably persistent bleeding even in a healthy person.

Acute ulcerative stomatitis (Vincent's infection).—The gums bleed freely and are *painful.* There is a characteristic offensive odour. Small yellow sloughs appear at the tips of the interdental papillæ. These sloughing ulcers may spread along the gums and may occur also on the mucous membrane of the other parts of the oral cavity.

Treatment: The ulcerated areas are dried and painted sparingly with 20 per cent. chromic acid in water, followed after one minute by hydrogen peroxide (20 vols.). This treatment is repeated on three successive days, and a peroxide mouthwash is prescribed instead of a toothbrush. If a cure, or at least great improvement, is not achieved at the end of this period, the case should be referred to a dentist, provided that agranulocytosis has been excluded.

Subacute marginal gingivitis.—This is by far the most common pathological cause of bleeding. A thin red line and swelling are seen at the gum margin, and the interdental papillæ are swollen and inflamed. The gum margins bleed freely when touched, but there is no pain. If the condition is not treated, bacteria, food and tartar accumulate between the teeth and the gums. Ulceration occurs with detachment of the gum from the teeth and the disease progresses to pyorrhœa.

Pyorrhœa.—Bleeding occurs less frequently, but the condition is more serious in its effects, and adequate treatment may necessitate gingivectomy or dental extractions. A fine probe can be passed between the teeth and the gum into an ulcerated pocket. Debris, blood, and beads of pus may be expressed by pressure on the pockets. From time to time mastication squeezes infected material into the

parodontal tissues with the formation of abscesses (gumboils). Pyorrhœa also gives rise to absorption of alveolar bone in the vicinity, resulting in loosening and loss of teeth, or in the teeth becoming devitalized.

Gingivitis may seem a trivial disease, but it often progresses to pyorrhœa. The possible *complications of pyorrhœa* are therefore mentioned below in order to emphasize the importance of treatment at an early stage when a cure can be effected by simple means. Halitosis may cause social embarrassment. Apart from physical discomfort, the wearing of dentures may have a profound psychological effect, especially in young women. There is strong evidence that suppuration in the lungs may result from the inhalation of infected matter from the mouth. It is known also that bacteria and their products may be squeezed into the blood stream during mastication. Bacterial endocarditis may follow in cases of congenital or rheumatic valvular disease of the heart. It is not known whether the organisms and toxins entering the blood stream are responsible for some cases of arthritis or fibrositis. Analogy with a gonococcal focus of infection in the prostate suggests that such a possibility cannot be excluded. Clinical observation suggests that in some persons the loss of teeth leads to indigestion, and inability to chew thoroughly may play some part in the maintenance of peptic ulceration. A correlation has also been found between the condition of the teeth and gums and the incidence of carcinoma of the stomach. Finally, it is possible that the presence of a considerable area of ulceration in the mouth may have some effect on the general health, e.g., the insulin requirement of diabetic patients is greater in the presence of infection.

The *treatment* of gingivitis and pyorrhœa is the province of the dentist. The mainstay of prophylaxis and after-care is that the gums should be brushed thoroughly and regularly. The gingival epithelium responds to friction by becoming tougher, just as the hands of a manual labourer become horny. Thus the liability to minor injuries is reduced and an efficient barrier to infection is presented.

Neoplasms.—Tumours of the gums will be evident on examination, and bleeding is not likely to be the sole complaint of the patient.

THE GENERAL CAUSES OF BLEEDING GUMS

In all cases of gingivitis systemic factors lowering the resistance of the patient should be considered. Well known among these are dietetic deficiency, anæmia, uræmia, diabetes mellitus, mercury or bismuth poisoning, and hormonal disturbances occurring during pregnancy, menstruation and adolescence in girls. The infection is less frequent and may heal more readily in those leading a healthy existence.

Several rare disorders of the blood or of the capillaries may also give rise to bleeding gums. It is of the utmost importance to the patient that a correct diagnosis should be made early, and especially before any vigorous treatment is given. The principal diseases to be considered are acute leukæmia, agranulocytosis, thrombocytopenic purpura, scurvy, other hæmorrhagic states, and occasionally chronic myelogenous leukæmia. Agranulocytosis especially should be considered when the local condition fails to improve as soon as treatment is instituted. These other diagnoses should be considered if the patient looks ill or if additional clinical features such as purpura or anæmia are evident. In such cases a full clinical examination should be made, including the family history and the patient's diet.

It may be necessary also to investigate the total and differential leucocyte counts, the number of platelets, and the bleeding and clotting times. It is clear that in most cases such investigations are rendered unnecessary by clinical examination of the mouth and the general appearance of the patients.

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THE USE AND ABUSE OF EAR DROPS

THERE is a great diversity of methods and drugs for the treatment of otitis in one or other of its forms, but the method of treatment is still of more importance than the type of medicament used in the ear canal, although many of the methods are too time consuming for use in ordinary hospital or general practice. The introduction of State Medicine has in many cases lessened the time which may be given to each patient, but the temptation to prescribe ear drops without any indication as to how they are to be used should be resisted. A sheet of simple printed directions handed to the patient after a short explanation of the procedure will usually do a great deal to enhance the value of the treatment, although there will be a few patients who do not understand it completely. The patient should understand that it is worse than useless to try to place drops in an ear from which the discharge is so profuse that they will be rapidly washed out again, and also the importance of removing any thick pus or debris present in the deep meatus which might prevent solutions reaching the site of origin of the discharge.

MEATAL SKIN INFECTIONS

In acute infections of the skin of the external auditory meatus swelling prevents the instillation of ear drops and it is better to use a solution soaked into $\frac{1}{2}$ in. self-edged gauze which should be worked gently into the canal. A saturated solution of aluminium acetate in water (approximately 8 per cent.) helps to reduce the swelling and relieve the pain. After the acute stage is over the meatus should be syringed to remove all debris and the meatal walls painted with 2.5 per cent. gentian violet in spirit, or 2 per cent. salicylic acid in spirit, used as drops. In the less acute cases oily drops are useful: one part of dilute mercury nitrate ointment in nineteen parts of almond oil. Chronic infections of the canal met with in this country usually respond well to the gentian violet paint and, as recurrence is frequent, followed for some months by 2 per cent. salicylic acid in spirit.

OTITIS MEDIA

Before treatment of *acute suppurative otitis media* is started it is a good plan to take a swab of the pus for sensitivity tests of the organisms. Often no local treatment will be required in those receiving oral or parenteral chemotherapy, but if resolution is delayed and yet the organism is sensitive to the drug, irrigation of the meatus followed by spirit drops will be helpful. Many acute cases of otitis media resolve quite satisfactorily with chemotherapy without perforation of the drumhead, although for a short time 2.5 per cent. carbolic acid in glycerin, or one of the proprietary preparations which combine analgesic, hygroscopic and antibacterial properties, may be called for to relieve the pain.

Recurrent otitis media should not only be treated locally, for active measures against possible causes such as enlarged and infected adenoids, sinusitis, too forcible nose blowing with colds, and failure to keep water out of the ear, are of far greater importance. Hydrogen peroxide alone should not often be prescribed as ear drops as it is irritant in the meatus and may tend to keep an infection active. One per cent. hydrogen peroxide in glycerin saturated with urea is a useful preparation in the chronic infections of the middle ear.

Locally applied, the antibiotics, like other drops, can have little value in acute otitis media and it is irrational to use local penicillin in chronic middle-ear infections as many of the organisms in the discharge are gram-negative. For chronic infection of the middle ear, streptomycin has little to recommend it as the discharge is rapidly found to contain resistant strains of organisms. Aureomycin would be of more value but is unstable in solution. A solution of chloramphenicol (chloromycetin) is neutral and stable, is active against gram-positive and gram-negative organisms and the large viruses. Therapeutic concentrations are non-toxic and, although the preparation is poorly soluble in water, a solution in propylene glycol is miscible with water as well as being hygroscopic.

Sensitivity to drugs used in the ear was not a factor of serious importance until the introduction of the sulphonamides and penicillin. Severe local skin reactions to these as well as most of the other antibiotics are seen not infrequently and are a complication for which it is essential to be on the alert. The patient should also be warned that on no future occasion should the substance to which he is sensitive be used in the ear or on any portion of his skin.

METHOD OF APPLYING EAR DROPS

The ear should be cleansed carefully and dried out with a wool mop, the final drying being often best carried out with surgical spirit. The patient lies on his side or sits in a chair and inclines his head; the auricle is pulled back and enough solution—which should be at body temperature—is used to half fill the meatus. The tragus is then pressed medially and backwards to drive the solution into the ear and expel bubbles. This head position should be maintained for five to twenty minutes and the drops allowed to find their own way out of the canal into a little wool placed to absorb the fluid but not to exclude air from the meatus. In most cases it is an advantage to allow free exchange of air between the ear canal and the atmosphere in order to encourage drying up of the discharge. Vertigo associated with the treatment is almost always a caloric response which is corrected easily, and is rarely related to increased intra-labyrinthine pressure as a result of an erosion into one of the semicircular canals.

INSTRUCTIONS FOR PATIENT

(1) Allow the bottle containing the drops to warm to body heat in a bowl of water at hot bath temperature.

(2) Cleanse the ear canal by syringing with water at body temperature used in a Higginson's syringe or by mopping with cotton-wool on a matchstick.

(3) Lie on the side with the affected ear uppermost.

(4) Pull the auricle up and backwards and run in the drops from a warm, clean teaspoon until the canal is half full.

(5) Press firmly on the skin elevation in front of the ear canal to force the drops into the canal.

(6) Remain in the position for five minutes.

(7) Allow the drops to escape on to the cotton-wool but do not leave wool in the ear as it is better for the canal to be exposed to the air.

Dizziness during treatment may be due to the use of solutions at the wrong temperature.

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NOTES AND QUERIES

Cutaneous Evidence of Rape

QUERY.—I recently examined three children between the ages of four and nine who allege that they were raped by an adult six days prior to examination. In two of them I found bruising of the vestibule which appeared as a red area well demarcated from the surrounding tissue. When this case comes to court I may be asked if these lesions are consistent with attempted forceful penetration occurring six days previously, and I would be grateful for advice on this matter, especially concerning colour changes of bruising in this area.

REPLY.—The marks left on tender skin by moist (as distinct from dry) chafing may be so slight as to amount to mere faint reddening which is so transient as to elude detection if not seen within twenty-four hours. Swabs (for foreign mucus, hairs, semen or seminal fluid—to be detected by the phosphatase test, or specific bacteriological infection) may be the sole means of proving an offence. Therefore to see reddening six days after an alleged assault implies rougher treatment, possibly with slight infection of the cutis. It is, of course, important to exclude digital and swab or other application, local antiseptic or dressing reaction, in order to be ready for cross-examination: use of words such as 'consistent with' rather than 'due to' will avoid trouble whilst according the prosecution all the help they can reasonably expect.

KEITH SIMPSON, M.D.

Actinotherapy

QUERY.—(a) I shall be greatly obliged if you will let me know what is the current opinion on actinotherapy.

(b) Is general ultra-violet irradiation considered to have any real therapeutic action, and if so, in what conditions?

(c) Certain writers on the subject consider that the high-amperage carbon or tungsten arcs have definite therapeutic advantages over the mercury arc—is this the general opinion?

(d) I have recently tried to buy a high-amperage carbon arc lamp, but three manufacturers to whom I have written say they have discontinued the manufacture of such lamps, owing to lack of demand.

(e) With reference to infra-red therapy, I understand that the rays from a luminous source, such as the 1000 watt tungsten filament glass bulb, are considered to penetrate the tissues more deeply than rays from a 'black-body' emitter. Is this so in actual clinical practice? Has the luminous source any real thera-therapeutic advantage over the 'black-body' emitter?

REPLY.—(a) The vogue of actinotherapy has greatly decreased although I personally still use it quite a lot in selected cases. It is, of course, possible that the wave of therapeutic nihilism which is at the present moment with us accounts for this negative phase.

(b) The tonic action of ultra-violet irradiation does not in fact exist when one reads between the lines of the statistics. I feel, however, that there must be some therapeutic action; there is undoubtedly one in such conditions as psoriasis, in particular, when used in conjunction with coal tar ointment. Its use in rickets and lupus has of course greatly decreased since the advent of calciferol and adequate diet.

(c) There is no doubt that high-amperage carbon or tungsten arcs have advantages over the mercury vapour arc. It would seem that any beneficial effect which exists, as for instance in psoriasis itself, results from the longer rays such as occur in the sun spectrum.

(d) It is true that these high amperage carbon arc lamps are no longer being made, but I believe that in the near future a good substitute will be found in fluorescent lamps which give out ultra-violet rays of wave lengths longer than 2,800 angstrom units. I am at present experimenting with these and have found them very satisfactory.

(e) It is quite true that radiations from sources rich in visible rays have a more penetrating

effect than non-luminous generators. This is due to the fact that rays around the wave lengths of the red end of the spectrum are not stopped by water, whereas the long infra-red rays emitted by the black-body emitter are rapidly absorbed by water. P. BAUWENS, M.R.C.S., L.R.C.P.

Epileptiform Attacks in Premature Infant

QUERY.—A Cæsarean baby, six weeks premature, is now aged thirteen months. He has not cut a single tooth; he refuses to crawl but is willing to try walking when held up. He does not utter one articulated word, not even 'daddy'. Every three weeks, almost to the day, he has a bout of cyclical vomiting, starting with swaying of the head and rolling of the eyes, without an outright convulsion. He sleeps after the vomiting: then his skin and lips alternate from pallor to redness, on and off, for some time. The next day he is normal and ravenous for food, which is similar every day and includes cod-liver oil and orange juice. Is a high protein diet indicated or does this case point to a minor epilepsy?

REPLY.—The first point to be considered is this child's development. Although some children begin walking early without passing through the preliminary crawling stage, others do not achieve it until eighteen months of age, whilst speech is generally acquired between the age of twelve and twenty-four months. The failure to crawl and speak in this case at thirteen months is not necessarily unusual so long as the other steps in development, such as head raising, sitting and standing have been normally achieved. Without such information it is difficult to assess this particular child's progress.

Despite the periodicity and prominence of vomiting the possibility of the attacks being epileptiform should first be considered, and confirmed by electroencephalography, before any gastro-intestinal or other cause is sought. The age at which the attacks began is not stated but if within the first six months of life an intracranial birth injury is the most likely cause, especially in a premature infant, even though born by Cæsarean section. When the attacks start after six months and are few in number acute infection should be excluded as the cause, whilst infantile tetany is unlikely with a normal diet which has included cod-liver oil.

Presuming the epileptic nature of this condition, phenobarbitone in small doses such as ½ grain (8 mg.) thrice daily should be tried. A high protein diet by the addition of glutamic acid has been advocated for mentally retarded children, but there is no definite evidence that such a diet does significantly influence their mental function and it would not seem to be indicated.

O. D. FISHER, M.D., M.R.C.P., D.C.H.

Reading Difficulties

QUERY.—I have a patient, a boy aged eleven, who has found it impossible to learn to read words of more than two syllables. This difficulty is apparently due to inability to associate the written symbol with the spoken word. He has made up for this by learning by ear, and so far has been able to keep pace, more or less, with other boys of his own age. Recently, however, he has shown signs of giving up the struggle and is exhibiting choreiform movements and (increasing) nail-biting, with outbursts of temper and weeping. Physically, he is a well-developed and healthy child, and I have found no other mental backwardness or disorder except that he is left-handed and has a right master eye. Is there any means of teaching him to read, preferably at home, or any advice which would help his schoolmaster to teach him?

REPLY.—In this case a diagnosis has apparently been made that the boy is suffering from a neurosis caused by a specific reading disability, and not by a generalized mental defect. It would be necessary to confirm this diagnosis by further investigation, especially of the patient's intelligence and home background.

Teaching at home by parents is not to be recommended. Remedial teaching of reading is a skilled job, which depends as much on the establishment of good relations between teacher and pupil, as it does on the knowledge of useful methods. In most cases the parent is unable to be sufficiently detached emotionally to be successful, nor is he likely to have the necessary knowledge. If possible, the child should be referred to the local Child Guidance Clinic, where the educational psychologist would be able to suggest a suitable teacher, either under the Local Education Authority, or privately. If this is impossible, then his schoolmaster may be prepared to give up at least half an hour a day to the boy. The schoolmaster should be acquainted with the following publications:—

Schonell, F. J.: 'Backwardness in the Basic Subjects', Oliver and Boyd, chapters 7, 8, 9, 10, 11.
——'The Psychology and Teaching of Reading', Oliver and Boyd.
Pamphlet No. 18: 'Reading Ability', H.M.S.O.
Gates, A. I.: 'The Improvement of Reading—a Programme of Diagnostic and Remedial Methods', Macmillan.
Scottish Council for Research in Education: 'Studies in Reading', vol. 1, 1949.

A. SPENCER PATERSON, M.D., F.R.C.P.ED., D.PSYCH.

Rose's Test in Rheumatism

QUERY.—Can you give me information about

the 'Rose Test'? I believe it is used in the diagnosis of rheumatoid arthritis. What is its precise value?

REPLY.—The test was re-introduced by Rose in 1948 as a means of distinguishing rheumatoid arthritis from similar clinical states. In this country, Ball (1950) and Clark (1951) have published further results. Pike (1949) has analysed the nature of the responsible factor in serum.

It appears that in different hands the test gives a positive result in from 25 to 90 per cent. of cases of established rheumatoid arthritis. It is occasionally positive in other illnesses, but seldom in ankylosing spondylitis, and its most valuable use is probably in helping to differentiate true ankylosing spondylitis from rheumatoid arthritis. There is little or no correlation between Rose's test and the severity of the disease, sedimentation rate, hæmoglobin, plasma viscosity, turbidity tests, and so forth. The full differential test is performed as follows:—

A specimen of serum is inactivated and any normal heterophil antibody absorbed out with normal washed sheep red cells. The agglutinin titre of this absorbed serum to sheep red cells sensitized with rabbit anti-sheep red cells serum (normal Wassermann reaction amboceptor) is determined in the normal way by adding a volume of sensitized sheep red cells to a series of twofold dilutions. Readings are taken at two or four hours and then overnight. A sensitized red cell agglutinin titre of greater than 1/32 is usually considered positive.

B. W. LACEY, M.D., B.SC.

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Ball, J (1950): *Lancet*, **ii**, 520.
Clark, C.J.M. (1951): *Ann. rheum. Dis.*, **10**, 232.
Pike, R.M., *et. al.* (1949): *J. Immunol.*, **63**, 441, 447.
Rose, H.M., *et. al.* (1948): *Proc. Soc. exp. Biol., N.Y* **68**, 1.

PRACTICAL NOTES

Sulphonamides in Cervical and Vaginal Infection

A 'clinical evaluation' of a sulphonamide preparation known as 'triple sulpha cream' in 110 patients with cervicitis, three with cervical polypus, 19 with cervical erosion, and 71 with vaginitis has been made by A. Jacoby *et al.* (*American Journal of Obstetrics and Gynecology*, June 1952, **63**, 1349). The cream is a combination of sulphathiazole 3.42 per cent., N'acetylsulphanilamide 2.86 per cent., N'benzoylsulphanilamide 3.7 per cent., and urea peroxide 1 per cent. in a jelly (cream) base. The patients with cervicitis were all treated by cervical cauterization, coagulation, or conization. Following this, the sulphonamide cream was applied as follows:—

'A plastic vaginal applicator of 5 c.c. capacity was filled by screwing the end on to the screw top of the tube of cream. By pressing on the base of the tube the plunger of the applicator was displaced until the barrel was filled. The barrel was disconnected from the tube and the tip of the applicator inserted between the labia into the vagina for about one inch. The plunger was then depressed depositing the contents within the vagina'.

The patients were seen on alternate days for the first fortnight; then once weekly until healing had occurred. On each occasion 'the vagina was cleansed and a cotton-tipped applicator saturated with mercurochrome was introduced into the cervical canal'. The average time for complete healing was five to six weeks, compared with four months for a previous group treated by the same method but without sulphonamides. In the 71 patients with vaginitis the sulphonamide cream was applied daily in the same way, and the inflammatory changes and symptoms disappeared in 49 of these patients in an average of three to four weeks of treatment. Of the 38 patients with Trichomonas infection in this group, 24 were 'cured', 5 'improved' and 9 'unimproved'. It is considered that in the Trichomonas group 'the improvement probably was a result of the elimination of concomitant bacterial agents rather than the destruction of the trichomonads'. Local irritation from the use of the cream occurred in two cases.

Treatment of H. Influenzæ *Meningitis*

As a result of their experience with 18 patients with 'bacteriologically proved meningitis due to *H. influenzæ*', M. H. Lepper *et al.* (*American Journal of Diseases of Children*, June 1952, **83**, 763) conclude that 'aureomycin used alone is a successful form of therapy in meningitis due to *H. influenzæ* and that no additional advantage is gained by using streptomycin and gantrisin in addition'. Three other points are stressed by these workers: (1) 'When aureomycin is used alone, the dose should be at least 50 mg. per kilogram every 24 hours and early treatment should be by the intravenous route'. (2) 'With the use of aureomycin, deaths from influenza bacillus meningitis should be uncommon, but there is still room for improvement in results as far as morbidity and permanent nervous-system damage is concerned'. (3) 'Penicillin when given in sufficient dose may be effective in some patients with *H. influenzæ* meningitis',

but they do not feel that 'it is the drug of choice or likely to become so'. The dosage schedule for aureomycin consisted of 50 mg./kg. intravenously during each 24-hour period. 'After one or two days of intravenous therapy, 12.5 mg. per kilogram was given by mouth at six-hour intervals. After 24 hours of combined oral and intravenous therapy, intravenous administration was stopped, and the patients continued with oral medication.'

Cortisone in Osteoarthritis of the Hip

THE effect of cortisone in 10 cases of degenerative disease of the hip has been investigated by W. F. Dowdell, W. M. Solomon, R. M. Stecher, and R. Wolpaw (*Annals of the Rheumatic Diseases*, June 1952, **11**, 168). The patients, five women and five men, were aged forty-eight to seventy-six years, and pain referable to one or both hips had been present for one to five years in 50 per cent. of them, and for six to thirty-two years in the remainder. After a preliminary twenty-two days of placebo treatment, the patients were given cortisone by mouth in the following daily doses, the daily dose being given in divided doses every six hours: 300 mg. on the first day, 200 mg. on the second, and then 100 mg. daily for twenty days. Subjective improvement was noted in six patients while taking the placebo and in eight while taking cortisone; this consisted in a sense of well-being, less pain, less stiffness and a feeling of ease on walking. It was usually more marked in the cortisone-treated patients. Objectively 'the increases in mobility noted in the ten patients during both placebo and cortisone periods were essentially the same. On critical analysis, the objective improvement noted during the placebo period was slightly greater than that observed during the cortisone period.' It is therefore concluded that 'the routine use of cortisone in malum coxæ senilis cannot be recommended in view of the small improvement observed in the ten patients studied'.

Methyl Testosterone in Premature Infants

BECAUSE of its action in promoting nitrogen retention, testosterone has been suggested as of possible value in the treatment of premature infants to promote a more rapid gain in weight. According to Ursula James and B. L. Coles (*Archives of Disease in Childhood*, June 1952, **27**, 265), however, 'this hormone is of no value in the rearing of healthy premature infants'. This conclusion is based upon the results in two groups of premature infants. In one group of 50 such infants, 26 received 'casinal' (a protein concentrate), 1 g. per lb. birth weight daily, whilst 24 received the same amount of 'casinal' together with 5 mg. of methyl testosterone daily by mouth. Treatment was continued until the infant was discharged from hospital or for twenty-eight days. The control group consisted of premature infants born in the same unit in 1948-49 and subject to the same feeding methods. The other group consisted of 25 premature infants in another hospital, 10 of whom received 5 mg. of methyl testosterone daily by mouth, whilst the remainder acted as a control group. 'No significant difference in the time taken to regain birth weight or the amount of weight gained over birth weight at 1 month was noted between the treated cases and the controls in any weight group.' Nor was there any evidence that 'the addition of protein to standard feeds' enhanced the action of testosterone. 'No side-effects were noticed as a result of treatment apart from transient enlargement of the clitoris in two cases', and it is considered that methyl testosterone 'appears safe for administration to premature infants in the dosage employed'.

Y-Shaped Adaptor for Intravenous Therapy

A Y-SHAPED adaptor for use in administering intermittent thiopentone, flaxedil, or nitrous oxide-oxygen anæsthesia, is described by M. E. Samrah, of Brighton General Hospital (*British Journal of Anæsthesia*, July 1952, **24**, 227). The adaptor is fitted with taps at the distal ends, and the common stem is joined to a French's needle (fig. 1) which is left in the vein during the operation. The syringe, containing

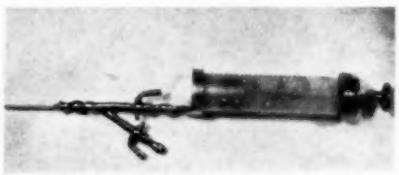

FIG. 1.

thiopentone, or other fluid, is joined to one stem of the adaptor and 'held firmly to the forearm with the aid of the "Third Hand" devised by Magill; the remaining branch is left free with tap closed'. The advantage claimed for this Y-shaped adaptor is that it saves disconnecting the syringe from the needle or using another vein for additional intravenous injection during an operation; and the use of a

French's needle 'diminishes the possibility of a blockage formed by a blood clot during anæsthesia'. Intravenous injections of *d*-tubocurarine chloride, and transfusions of blood, saline or plasma, may also be administered by the Y-shaped adaptor.

PAS in Intestinal Tuberculosis

As a result of his experience with three patients (aged 42, 27, and 24) with extensive bilateral pulmonary tuberculosis and intestinal tuberculosis, I. N. Wolfson (*Annals of Internal Medicine*, June 1952, **36**, 1475) concludes that 'PAS is a useful drug in the treatment of intestinal tuberculosis'. PAS was given in the form of the sodium salt in daily doses of 12 to 16 grammes, depending upon the tolerance of the patient to the drug. Treatment was continued for four months in two cases and for five months in the third. 'Troublesome reactions' occurred in one case, consisting of lower abdominal cramps and diarrhœa; these reactions disappeared when treatment was temporarily suspended. The most striking change was the marked radiological improvement which occurred in all three cases. Clinical improvement began within a few weeks of starting treatment. Abdominal pain disappeared within one or two months of instituting treatment in two cases, whilst in the third it was reduced to 'very mild gaseous distension' within five months. All showed a gain in weight, ranging from 8 to 17 pounds, soon after treatment was begun. It is concluded that the use of PAS 'is indicated in streptomycin-resistant patients, in patients allergic to streptomycin, and in patients from whom it is desirable to withhold streptomycin in order to maintain streptomycin sensitivity for the future management of the pulmonary disease'.

Barbiturates and Isoniazid

Among the more troublesome side-effects of isoniazid (isonicotinic acid hydrazide) are the hyper-reflexia, twitching of the legs, vertigo and insomnia, which are attributable to stimulation of the central nervous system. S. Y. P'an *et al.* (*American Review of Tuberculosis*, July 1952, **66**, 100) report that 'phenobarbital or pentobarbital are able to protect animals, mice and dogs, against isoniazid convulsions and death'. This 'antagonistic effect of the barbiturates against the central nervous system stimulating effect of isonazid', they consider, 'suggests that, in patients receiving isoniazid treatment and manifesting symptoms suggestive of central stimulation, such as hyper-reflexia, leg twitching, insomnia, et cetera, phenobarbital administered in small doses simultaneously with isoniazid may be of help in preventing these symptoms'. Phenobarbital is preferred to pentobarbital for this purpose as 'the maximal action of both isoniazid and phenobarbital are reached at approximately the same time'. For 'immediate or quick relief of acute toxic symptoms of central stimulation after they had manifested themselves' they recommend the quicker-acting pentobarbital.

Effect of Antibiotics on the Oral Tissues

In an article dealing with drugs affecting the oral tissues, H. H. Stones (*Medical Press*, July 23, 1952, **228**, 86) devotes a considerable section to the antibiotics. *Penicillin* lozenges, if used continuously, and also atomized aqueous solutions, may cause an oral reaction in the form of discoloration of the tongue and, less frequently, glossitis and stomatitis. The occurrence of stomatitis in patients receiving *streptomycin* is stated to be rare, but vesicular eruptions of the lips and buccal mucosa have been reported. Both *aureomycin* and *chloramphenicol* produce lesions of the oral mucosa 'in 10 to 40 per cent. of cases'. Xerostomia, angular stomatitis, glossitis, and black hairy tongue may develop in sensitive subjects, and in addition 'irritation of the rectal, perineal and, more frequently in females, of the genital regions'. These changes are similar to those which occur in deficiency of the vitamin B complex, and particularly of riboflavin, and have been noted to be less severe in those who receive vitamin B supplements. The symptoms may persist for some time after discontinuation of administration of the antibiotics. *Terramycin*, which is usually administered by mouth, is stated to produce similar changes. An interesting finding is that the reddish-orange fluorescence of the tongue which is normally visible under screening with Wood's glass, disappears when antibiotics are given orally. 'This occurs with penicillin lozenges . . . , with specially prepared streptomycin lozenges and with chloramphenicol. Similar results are achieved with aureomycin though not until treatment has ceased, as this antibiotic in itself produces a bright yellow fluorescence over the whole of the dorsum. On the other hand, sulphathiazole lozenges have no effect.'

Cortisone in Schizophrenia

The effects of cortisone in schizophrenia have been studied by L. Rees and G. M. King (*Journal of Mental Science*, July 1952, **98**, 401). The study was made in 12 patients, divided into six pairs matched for age, sex, clinical status, duration of illness and previous treatment. For a week all were given injections of

sterile water. During the next week one member of each pair was given cortisone intramuscularly in divided doses: 300 mg. on the first day, 200 mg. on the second, and 100 mg. on the third and fourth days. The other member of each pair was given injections of sterile saline. 'No significant improvement was noted in the patients receiving cortisone therapy by clinical observation or by means of psychiatric rating scales'; neither was there any change in the electroencephalogram. One patient became temporarily worse while receiving cortisone. All the patients receiving cortisone showed a marked fall in the circulating eosinophils.

Poisoning by Umbillifers

THE toxic potentialities of umbilliferous plants are reviewed by Peter Cooper (*Pharmaceutical Journal*, July 5, 1952, **169**, 18). In Great Britain the important members of this group are the hemlock water drop wort (*Œnanthe crocata*), cowbane or water dropwort (*Cicuta virosa*), horsebane (*Œnanthe phellandrium*), and the spotted hemlock (*Conium maculatum*). All grow along the banks of rivers in the summer, and the hollow stems have for long been popular with boys as peashooters or even as substitutes for cigarettes for smoking purposes. The poisonous principles of the first three of these plants are œnanthotoxin and cicutoxin, which act on the spinal medulla and cause stupor, delirium and convulsions. Treatment of poisoning by these consists of gastric lavage and the administration of chloral hydrate and bromides. 'After sedation, stimulants are administered.' It is suggested that 'injection of a quick-acting barbiturate might be effective, since the intoxication is of the picrotoxin type'. The main constituent of the spotted hemlock is coniine, which causes progressive loss of muscle power, loss of sight, loss of the swallowing reflex and finally respiratory paralysis. Treatment consists of gastric lavage followed by the administration of tannic acid or charcoal and warmth and respiratory stimulants. If asphyxia threatens, artificial respiration is indicated. Attention is also drawn to the giant hog-weeds, of the *Heracleum* species, brought into this country from Asia and eastern Europe as garden curiosities, and now found growing wild in Surrey and Middlesex. No case of poisoning from ingestion of these has been recorded, but contact with them may cause dermatitis and pyrexia. It is also reported that plants of *Ammi majus*, a native of the Nile delta, have been found on the banks of the Severn. One of its constituents, ammoidin, is known to cause nausea and vomiting and coma when the plant is eaten.

Glutamic Acid in Mental Deficiency

THE results of the administration of glutamic acid to fifteen 'feebleminded, maladjusted' boys, aged ten to fifteen years, with an I.Q. of 54 to 76, has been studied by Martha Foale (*Journal of Mental Science*, July 1952, **98**, 482). The glutamic acid was given in the form of tablets, each containing 0.5 gramme of the naturally occurring dextro-rotatory substance. The daily dose was 9 g. (6 tablets t.d.s.) for the first four months, and 12 g. for the subsequent six months. There were no side-effects. The cost of treatment for the glutamic acid was £1 per patient per week. A comparable group of 15 boys was used as a control group. Four of the treated boys gained in I.Q. from 8 to 11 points; the comparable improvement in the control group was negligible (2 to 3 points). There was no difference between the two groups in the gain in P.A. (practical ability) as measured by the Passalong Test. In eight of the treated boys there was a definite improvement in general adjustment: 'their behaviour was improved, they were more alert, self-confident and showed more interest, while none of the control boys showed such marked changes'.

Hepatitis in Doctors

THE incidence of hepatitis in doctors has been investigated by Sten Madsen (*Ugeskrift for Laeger*, July 17, 1952, **114**, 951). The findings are based upon a questionnaire sent to all the doctors and lawyers in Denmark (i.e., 4,700 doctors and 2000 lawyers), 1,570 hospital nurses and 2,200 industrial employees. Considering only those individuals over the age of 18 years, the incidence of hepatitis was: 10.4 per cent. in doctors, 7 per cent. in lawyers, 6.8 per cent. in nurses, and 3.9 per cent. in industrial employees. 'Doctors are thus significantly the most frequently attacked'. Doctors and lawyers were attacked more frequently between the ages of twenty-five and thirty-five—a later age-incidence than in the case of nurses and industrial employees. The incidence was the same in males and females. The probable cause of the higher incidence in doctors is considered to be infection acquired in hospital. 'No medical speciality showed itself particularly endangered, nor was this the case with personnel in laboratories or post-mortem rooms.' An attack in childhood seemed to confer a certain amount of immunity and, as assessed by the duration of jaundice, the severity of the disease increased with age. The relapse rate in doctors was 5 per cent.

REVIEWS OF BOOKS

Diseases of the Ear, Nose and Throat. Vol. 1 and 2. EDITED BY W. G. SCOTT-BROWN, C.V.O., M.D., B.CH., F.R.C.S., LONDON: Butterworth & Co. (Publishers) Ltd., 1952. Pp. xv and 756 (index 47) and xv and 639 (index 47). Figures 338 and 260. Price £8 8*s*. the 2 volumes.

THIS work in two large volumes covers the whole field of ear, nose and throat diseases. It is handsomely produced and well illustrated. Thirty-two writers contribute. With so many authors a certain amount of overlapping is bound to occur, and in places this is rather obvious. The editor in his introduction expresses the hope that the individuality of the articles will give a more stimulating approach to the subject in spite of this overlapping of subject matter and differences of opinion, and on the whole this is the case. The anatomy and physiology of each section are carefully described. These contributions should prove most useful, especially to those taking the higher examinations in this specialty. A large part of the second volume is devoted to the œsophagus and the trachea and bronchi. These two sections deal exhaustively with these subjects; illustrations are on a lavish scale, and altogether these contributions should be of great value. The sections on ear diseases by various contributors are very well done and they present a complete and up-to-date picture of present-day opinions and practice. It is good to see malignant diseases of the ear, nose and throat dealt with so satisfactorily. So often descriptions are rather sketchy, but here in all cases descriptions and recommendations for treatment are complete and in accord with the latest views. Almost every contributor has given an extensive bibliography of the subject about which he writes and in a book of this sort this is invaluable. The two volumes worthily present the outlook and practice of British otolaryngology at the present time.

Angiocardiography (*Annals of Roentgenology*, Vol. 20). BY C. T. DOTTER, M.D., and I. STEINBERG, M.D. London: Cassell & Co., 1952. Pp. xii and 304. Figures 252. Price £5 18*s*. 6*d*.

IN the last decade a number of technical procedures have emerged from the experimental stage to play their part in the day-to-day diagnostic investigation of cardiac patients. Among these, angiocardiography holds an important place. One therefore hails as important the appearance of an authoritative and lavishly illustrated book by experts whose experience of the method is particularly extensive. In angiocardiography a quantity of radio-opaque substance is injected rapidly into an arm vein, and by suitably timed x-ray exposures its progress is traced through the heart and great vessels. The method obviously affords a means of delineating individual chambers of the heart with a precision hitherto unattainable, and can give detailed information regarding the pulmonary vessels and the aorta.

The authors describe in detail the technique and apparatus employed, and discuss fully and fairly the dangers inherent in the method. Quoting from their own experience, they describe the findings in normal individuals, and the changes recorded in cardiovascular disease and in a number of pathological lesions of the lungs and mediastinum. The scope of the book is impressive, covering not only the usual field of congenital heart disease, but the segmental anatomy of the pulmonary arteries, the appearances in myocardial infarction and pericarditis, in pulmonary tuberculosis and bronchial carcinoma, and many other conditions. The reviewer was particularly impressed by the value of this procedure in cases of early silent syphilitic aortitis, in which changes in the calibre in the vital first inch of the aorta could be demonstrated—a task beyond the powers of conventional radiography or clinical examination.

The standards of description and illustration are uniformly high. Space might have been saved by the omission of the simple descriptions of pathology and anatomy in individual cardiac and pulmonary lesions, although these may be of value to non-specialist readers. One might cavil, too, at the statement (p. 144) that 'at present the diagnosis of coronary artery disease is primarily based on the electrocardiogram'. Throughout, the authors maintain a judicial and balanced outlook which is as rare as it is refreshing. The sponsors of a new technique are apt to push its claims far beyond the limits which are eventually set by experience. Dotter and Steinberg, however, continually review their results against those obtainable by simpler or less dangerous methods. They state bluntly that angiocardiography 'is not indicated in the routine investigation of well-established mitral stenosis'; 'is rarely of necessity in the study of clinically characteristic cases of patent ductus arteriosus'; and in the section on congenital heart disease they set out 'to indicate the findings, usefulness *and limitations*' of the method. The section entitled 'The decision to perform angiocardiography' merits careful study by all who use the method. The volume is one

which should be read, not only by all who are interested in this field, but by physicians who have to handle cases of intrathoracic disease.

Cardiac Emergencies and Heart Failure: Prevention and Treatment. By A. M. Master, M.D., M. Moser, M.D., and H. L. Jaffe, M.D. London: Henry Kimpton, 1952. Pp. 159. Figures 13. Price 22*s*.

This is a first-class publication which contains a wealth of practical information. Short treatises are apt to be disappointing when enlightenment is sought on treatment of a particular patient, but here we have compressed and attractively presented all details likely to be relevant. The authors have made it quite clear what they expect from each remedy and, like John Wesley of old, they have indicated when they have or have not tried it themselves. A list of drugs for the emergency bag is appended. A few case reports are interspersed in the text; a most commendable practice. Some rare but easily recognizable diseases are referred to and nearly 300 references are listed. The busy houseman and the general practitioner will find themselves well-armed with this up-to-date little book for which we have nothing but praise.

The Ciba Foundation Colloquia on Endocrinology, Volume 2. Edited by G. E. W. Wolstenholme, O.B.E., M.B., B.Ch. London: J. & A. Churchill Ltd., 1952. Pp. xix and 429. Figures 96. Price 35*s*.

The second volume of this series of four deals with papers and discussions held in 1950 at the Ciba Foundation on steroid metabolism and estimation. These conferences were attended by a select international band of highly specialized and technical expert workers, and naturally the reports on their deliberations are outside the scope of interest of most general medical readers. This is, nevertheless, the very reason why this book, with its verbatim reports of informal discussions, will be of real value to those who are actively engaged in these fields of research. In the first part there are papers on the estimation of urinary œstrogens, corticoids, 17-ketosteroids and the urinary metabolites of progesterone, whilst the second part is devoted to the breakdown of steroids.

Surgery and the Endocrine System. By James D. Hardy, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders Company, 1952. Pp. xii and 153. Figures 43. Price 25*s*.

The author has devoted half the volume to a general consideration of endocrinology in relation to surgery, beginning with a review of the body's response to stress, the alarm reaction of Selye. This complicated subject is dealt with succinctly and well. It is illustrated with ingenious diagrams designed to demonstrate the mechanisms at work under different conditions. These are good so long as the reader will remember that such diagrams cannot represent the whole mechanism: they therefore over-simplify. There are chapters on the dynamics of nutrition in relation to trauma, on the physiological basis of early ambulation, and on convalescence. In the second half of the book the anatomy of the various glands is given in detail, the different surgical procedures described and illustrated, and postoperative management and complications discussed. It is a well-presented and readable little book, and there is an excellent bibliography at the end of each chapter.

Clot Retraction. By O. E. Budtz-Olsen, M.D. Oxford: Blackwell Scientific Publications, 1952. Pp. xiv and 149. Figures 40. Price 25*s*.

This small monograph gives a comprehensive and thoroughly documented review of the literature of clot retraction. It is written by an enthusiast who has devoted himself to investigations in this field, and is amplified by the author's first-hand knowledge and by descriptions of his experiments. There is also a section on technical methods. Since the work deals with a highly specialized sector of knowledge it is likely to have only a limited appeal, but it should be highly valuable to all interested in problems of blood coagulation. The production is excellent, but the price is high for so small a book.

The Medical Inspection of School Children. By E. H. Wilkins, M.B., B.Ch. London: Baillière, Tindall & Cox, 1952. Pp. viii and 224. Figures 21. Price 16*s*.

The author of this book died in 1946, leaving the manuscript of his work unfinished. His colleagues in the school health service group considered the draft of such value as a summary of the school health service since its institution in 1907 that they decided to make themselves responsible for its publication. The book has been written in an attractive manner which makes its context easy to understand, not only by the experienced practitioner in the school health service, but it will also be useful to those who are studying for the Diplomas in Public Health or Child Health prior to entering the service. Dr. Wilkins has covered the field from the sociological background of the child to the

detailed findings of medical inspection, with special reference to education and environment. Although the book is in places rather sketchy, it does introduce many new and original ideas on the subject.

Mind and Life. By Sir Arthur Tansley, F.R.S. London: George Allen & Unwin Ltd., 1952. Pp. xii and 171. Price 15*s*.

These twelve essays on psychological subjects such as 'The energy of the mind' and 'The strength and weakness of psychoanalysis' by an eminent botanist let a welcome draught of fresh air into a stuffy, artificial, and sometimes verbose atmosphere. The biologist is in a position to study the ground floor of mind which too often those who study the upper stories are ignorant of or ignore. 'We can never understand the nature of the human mind if we ignore its origin from the minds of our animal ancestors who were not yet human' is written in the last essay, but that is the key-note to the book. There are no polemics in these essays; the point of view is put pleasantly, perhaps too pleasantly, but the effect is stimulating. In fact, the book is like a box of first-rate cigars; each essay starts smoothly, then as the simplifications expand the smoke tastes stronger and is more satisfying; they should be smoked slowly and it would be a crime to smoke more than one a day.

William Smellie. By R. W. Johnstone, C.B.E., M.D., LL.D., Edinburgh: E. & S. Livingstone Ltd., 1952. Pp. viii and 139. Figures 30, and frontispiece in colour. Price 20*s*.

It is appropriate that the present Professor-Emeritus of Midwifery in the University of Edinburgh should have written this short life and appreciation of his fellow-countryman whom he aptly describes as 'the master of British midwifery'. Two reasons are given for writing this new life of Smellie. The first is that it is sixty years since Glaister's 'Dr. William Smellie and His Contemporaries' was published, and it is now out of print. The other is 'the need for a comparatively brief account of Smellie and his work, which would keep as close as possible to the sparse facts, and avoid the numerous alluring side-issues presented by the history of eighteenth-century midwifery in Britain'. Professor Johnstone has adhered strictly to his brief, and practically half the book is taken up with a detailed analysis of Smellie's classical 'Treatise on the Theory and Practice of Midwifery' and his 'Set of Anatomical Tables'. The result is a work which will appeal predominantly to obstetricians. The book is written in that characteristically clear, but somewhat didactic, style in which the author over so many years initiated the medical students of Edinburgh to the mysteries of midwifery.

Klinik und Therapie der Vergiftungen. By Dr. Sven Moeschlin. Stuttgart: Georg Thieme Verlag, 1952. Pp. viii and 430. Figures 54. Price DM 45.

This is a well-written and well-illustrated book which contains an account of the author's personal experience of cases of poisoning from various causes, treated in the clinic of Zurich University. In addition to these personal observations, most of the modern literature on the subject is reviewed and references given at the end of each chapter. Not only are the symptoms well described, but the subject of therapy is dealt with. As the style is clear and the information up-to-date, this book will be useful, not only to the specialist, but also to any practitioner, whether he works in an industrial area, where various types of poisoning may occur, or in the country, where the increased use of chemicals has led to a greater possibility of poisoning and immediate therapeutic measures have to be considered.

NEW EDITIONS

Tropical Medicine, by Sir Leonard Rogers, K.C.S.I., C.I.E., M.D., F.R.C.P., F.R.C.S., F.R.S., and Sir John Megaw, K.C.I.E., M.B., D.Sc., in its sixth edition (J. & A. Churchill Ltd., 40*s*.), has been revised and brought up to date by the inclusion of new methods of diagnosis and treatment, and new drugs which have been developed since the appearance of the fifth edition in 1944. An example of this is the chapter on 'leprosy', in which treatment with the sulphones is described in full, and also new measures of prophylaxis. In these days of intercommunication by air travel, many tropical diseases are no longer limited to the countries where they are endemic, and practitioners will find a wealth of information on diagnosis and treatment in the new editicn of this well-known textbook.

Several new names are included in the list of contributors to *A Textbook on the Nursing and Diseases of Children*, by Various Authors, edited by Alan Moncrieff, M.D., F.R.C.P., in its fifth edition (H. K. Lewis & Co. Ltd., 37*s*. 6*d*.): Mr. David Matthews has written the section on burns, and has added a chapter on plastic surgery; the chapters on dietetics and infant feeding are by Dr. P. R. Evans, and that on diseases of the ear, nose and throat by Mr. James Crooks. A new chapter on bacteriology, by Dr. I. A. B. Cathie, has been added; and sections on thoracic surgery, physical medicine, medico-social work, and speech training are among the

new features. A word of praise is due to the producers of the illustrations, which are excellent, and include some attractive line drawings. The new edition enhances the already high prestige of this well-known and authoritative work on the care and nursing of sick children.

A NEW chapter on 'poisonous plants and fungi' has been added to *Forensic Medicine*, by Keith Simpson, M.D., in its second edition (Edward Arnold & Co., 21*s.*); this chapter replaces that on 'war gases' which appeared in the first edition. New legislation concerning Poison Laws and Industrial Injuries has been included; new drugs and insecticides added to the Poisons List; the dangers encountered by inhalation of poisonous fumes and the use of agricultural insecticides are discussed, and there is a useful section on food poisoning. The new edition of this authoritative and useful guide to forensic medicine, which is well illustrated, will prove useful to all practitioners and police medical officers.

Principles and Practice of Aviation Medicine, by Harry G. Armstrong, M.D., F.A.C.P., in its third edition (Baltimore: The Williams & Wilkins Co.; London: Baillière, Tindall and Cox, 57*s.* 6*d.*) has been enlarged by the addition of four chapters rendered necessary by the increasing use of, and development in, aerial travel. Although much of the book deals with the subject of aviation medicine from the point of view of aircraft personnel, with descriptions of the different examinations and tests, many of the chapters will have a wide general appeal, as for instance those on air and compression sickness, accidents, aerial hygiene and sanitation, air rescue and evacuation, the emotional reactions to flight, and the effects of aircraft noises. This is a most useful book and should be in the hands of all practitioners; as the author, who is Surgeon General, U.S. Air Force, states: 'In this air age, flying has become such an intimate part of our everyday life that all physicians should have a general knowledge of aviation medicine'.

The British Encyclopædia of Medical Practice, edited by Lord Horder, G.C.V.O., M.D., F.R.C.P. (Butterworth & Co. (Publishers) Ltd., 65*s.*), has now reached volume ten in the second edition. This volume stretches alphabetically from pituitary gland diseases to retinal diseases. It therefore devotes a considerable amount of space to psychiatry (twelve sections), and pregnancy; the puerperium and the placenta have also extensive sections devoted to them. It is interesting to find a tripartite authorship for pyelitis—a genito-urinary surgeon, a pathologist and a gynæcologist. Apparently this common condition no longer comes under the purview of the physician. The only disappointing section is that on rejuvenation; in a book such as this a little more practice and a little less philosophy would be more to the point.

IN the second edition of *The Science and Art of Joint Manipulation*, Vol. 2, *The Spinal Column*, by James Mennell, M.D., B.C. (J. & A. Churchill Ltd., 42*s.*), the author has incorporated his monograph on 'Backache', which has been extensively revised. The new material, on manipulation of the spine, follows on that contained in volume 1, which dealt with 'the extremities'. In order to aid those who have not studied the first volume the general problems of manipulation are discussed in the introduction. The illustrations in the new volume, which number 148, are well produced and are supplied with captions describing the different manipulative measures.

Architectural Principles in Arthrodesis, by H. A. Brittain, O.B.E., M.CH., F.R.C.S., in its second edition (E. & S. Livingstone Ltd., 42*s.*) reiterates the author's principle that a bone graft does not increase in thickness unless it is submitted to compression, a principle which underlies the method of hip-fusion associated all over the world with the name of Brittain. No one knows better how to do an operation than its originator, and herein is contained the author's own description of his own operation. He also describes the technique he uses for arthrodesing other joints. This book coming from the house of Livingstone's, it goes without saying that its format is superb.

Atlas of Human Anatomy, by Franz Frohse, Max Brödel, and Leon Schlossberg, in its new edition (George Allen and Unwin Ltd., 16*s.*), is a pocket size collection of anatomical drawings with a brief and simply written explanatory text. The majority of the plates are executed with the consummate draughtsmanship one expects from an artist of Brödel's attainments, but the reduced size has the effect of rendering much of the detail bewildering, and the colours are not very pleasing or life-like. It is difficult to decide for whom the book is intended. Certainly the medical student or practitioner would not find it particularly helpful or instructive, but it may be useful to nurses in training, or to laymen undergoing training in first aid or ambulance work.

The contents of the October issue, which will be a special number devoted to 'Advances in Treatment', will be found on page lxx at the end of the advertisement section.

Notes and Preparations, see page 313.
Fifty Years Ago, see page 319.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'BUTAZOLIDIN' brand of phenylbutazone, the sodium salt of 3,5-dioxo-1,2-diphenyl-4-*n*-butyl-pyrazolidine, has been prepared for the treatment of rheumatic diseases, and is stated to 'be effective both in the acute phases of rheumatic disease, and in the more chronic type of case'. The drug is rapidly absorbed and slowly excreted, so that a therapeutic blood level may be maintained 'for a considerable period after administration'. Indications for the use of 'butazolidin' include acute and chronic rheumatic affections of the joints. Issued in tablets containing 0.2 g., and in solution for injection, in ampoules of 5 ml. containing 1 g. of 3,5-dioxo-1,2-diphenyl-4-*n*-butyl-pyrazolidine. (Pharmaceutical Laboratories Geigy Ltd., Rhodes, Middleton, Manchester.)

'DINDEVAN' (phenylindanedione) is a synthetic anticoagulant for oral administration which has been prepared for use as a 'take-over' drug in cases of thrombosis or embolism after institution of initial therapy with heparin. It is claimed to be less expensive than heparin and to possess the advantage of being active by mouth, a therapeutic effect being produced within twenty-four hours and being sufficiently prolonged to maintain a satisfactory blood level on twice daily dosage; also elimination is stated to be sufficiently rapid to 'render cumulation a remote possibility'. Issued in scored tablets, each containing 50 mg. of phenylindanedione, in containers of 25 and 100. (Evans Medical Supplies Ltd., Speke, Liverpool, 19.)

'RAYSO' brand micro-fine barium sulphate has been produced for use in preparing suspensions for radiography. It is stated to be of 'uniformly small particle size which readily mixes with water to form a creamy suspension'. Advantages claimed for 'Rayso' are: its fluidity, which enables it to pass with ease through the teat of a feeding bottle for examinations in infants; no reflex nausea in adults; reduction in transit time of the test meal, and reduced risk of constipation following the meal. Owing to the fineness of the particles even distribution and penetration may be expected. Issued in composite drums of 1 lb., and in tins of 7, 14 and 28 lb. Also available in bulk. (Boots Pure Drug Co. Ltd., Station Street, Nottingham.)

PHARMACEUTICAL NOTES

'MYCOTA' is the new name given to 'Fungicidal Ointment and Powder' Boots. 'Mycota Ointment' contains undecylenic acid, 5 per cent., and zinc undecylenate, 20 per cent.; it is available in tubes of approximately 1 ounce. 'Mycota Powder', containing undecylenic acid, 2 per cent., and zinc undecylenate, 20 per cent., is issued in sprinkler tins of approximately 2½ ounces. (Boots Pure Drug Co. Ltd., Station Street, Nottingham.)

'TABLOID' brand PENICILLIN Products—Burroughs Wellcome & Co. announce that, in addition to the 20,000, 100,000 and 200,000 unit strengths already available, 'Tabloid' brand Penicillin, for oral administration, is now available in a strength of 500,000 I.U. per tablet, in tubes of 10 and bottles of 100, price 21s. and 180s. From July 21, 'Tabloid' brand Penicillin (Oral), 200,000 I.U., is reduced in price to 8s. 6d. per tube of 10. (Burroughs Wellcome & Co., 183-193 Euston Road, London, N.W.1.)

ROYAL ARMY MEDICAL COLLEGE LECTURES

A SERIES of lectures by well-known authorities on different aspects of medicine and surgery, of interest to both Service and civilian practitioners, will be held at the Royal Army Medical College from October 16, 1952, to April 23, 1953. Admission is free to all members of the medical profession. Full particulars can be obtained from the Commandant, Royal Army Medical College, Millbank, London, S.W.1.

KING EDWARD'S HOSPITAL FUND FOR LONDON

THE annual report for 1951 shows that the Fund has capital funds now amounting to between six and seven million pounds. In spite of crippling taxation and the abolition of the voluntary hospitals the Fund still receives legacies on a substantial scale. Receipts from this source in 1951 amounted to £131,000. In addition, a further sum of £80,000 was received from the executors of the late Viscount Wakefield of Hythe. The monies expended by the Fund have included grants to N.H.S. hospitals for purposes other than amenities, to hospitals and similar institutions outside the N.H.S., and to convalescent homes. The plans for providing homes for the aged sick are progressing steadily, and the allocation for the provision of twelve such homes has been increased to £350,000. The work of the emergency bed service, the hospital administrative staff college, the division of hospital facilities, the division of nursing, and the hospital catering advisory service are all reviewed. The mere retailing of the activities of the Fund is a most impressive demonstration of the outstanding service which the Fund is rendering to the improvement of the medical services of the country. (King

CONTINUED ON PAGE 314

Edward's Hospital Fund for London, 10 Old Jewry, London, E.C.2.)

BRITISH EMPIRE CANCER CAMPAIGN

THE annual report for 1951 may not make exciting reading but it records yet another year's steady, if slow, progress towards the elucidation of what has now come to be the outstanding major problem in medicine. No stone is being left unturned in the search for clues which may fit into the already established picture. It is probably a fair summing up to say that fundamentally the picture is becoming clearer, but the practical implications of this fundamental knowledge are still vague and sketchy. From the clinical point of view one of the more interesting features of this report is the reference to the work at St. Mark's Hospital, where examination of colectomy specimens removed by surgeons for the treatment of chronic ulcerative colitis has revealed unsuspected carcinoma in nearly 40 per cent. of those patients in whom the colitis lasted for more than ten years. (British Empire Cancer Campaign, 11 Grosvenor Crescent, London, S.W.1.)

PUBLICATIONS

St. Thomas's Reports, Vol. VII.—With the exception of a short note on acrylic lenses by Mr. Harold Ridley, the articles in this volume are contributed by junior members of the Hospital and Medical School staff. The eighteen articles cover a wide range of subjects, including the encephalogram of normal medical students, dicoumarol and tromexan therapy, chronic pneumonia simulating cancer, ulcers of the leg, and analysis of one thousand barium meal examinations. The volume is a tribute to the clinical research activities of the Hospital and deserves a wide circulation, and the Hospital authorities are to be congratulated on their foresight in encouraging the initiative of their younger men in this way. (St. Thomas's Hospital Medical School, London, S.E.1, price 10*s.* 6*d.*)

The Edinburgh Post-Graduate Lectures in Medicine, Volume V, 1948-49.—This volume contains the Honyman Gillespie Lectures for 1948 and 1949 given under the conditions of the Trust by graduates of Edinburgh. A very wide field is covered ranging from Incoordination of Uterine Action to Judgment in Cardiology, and there will be few readers who do not find more than one chapter that is of interest to them. Some of the sections are naturally already out-dated, but this does not apply to the majority, and the postgraduate for whom the lectures were intended will find much to profit him by the perusal of this book. It is well illustrated and remarkably cheap at its price. (Oliver and Boyd, price 21*s.*)

NAPT Handbook of Tuberculosis Activities in Great Britain and the Commonwealth.—The 14th edition of this comprehensive and valuable directory of hospitals, sanatoria, clinics, regional hospital boards, hospital management committees, local health services, and tuberculosis services in the British Commonwealth, will be welcomed by doctors, administrative officers, and social workers. Handsomely bound in dark red, it is some fifty pages larger than the previous edition, but the price (30*s.*) remains the same. (NAPT, Tavistock House North, London, W.C.1.)

Adelaide Hospital Centenary Book.—The Adelaide Institution and Protestant Hospital of Dublin was opened for the reception of patients in March 1839. Financial and architectural difficulties forced it to close its doors in June 1847 until October 1858, when it reopened with 68 beds. This centenary book, consisting of 131 pages (89 of which are advertisements which helped to make publication possible), and pleasantly illustrated, contains a number of appeals by eminent men, articles dealing with the history, development, and work of the Hospital, and an interesting contribution by Dr. J. D. Widdess on 'Dublin Hospitals—A Century's Progress'. (Parkside Press Ltd., 43 Parkgate Street, Dublin.)

IN his Foreword to *Cardiographic Technique*, by S. L. Barron, and A. Schott, M.D., Crighton Bramwell writes: 'Nowadays, the cardiologist is concerned chiefly with interpretation, and it is accordingly incumbent on his technician not merely to produce a high-class record suitable, if necessary, for publication, but also to master the fundamental physical principles of both electrocardiography and phonocardiography'. This little book describes these fundamental principles, and also deals with the subjects of extraneous interference and common faults, servicing, processing of photographic records, indexing and filing, and special cardiographic equipment. (Wm. Heinemann (Medical Books) Ltd., price 21*s.*)

The Circulation of the Blood, by William Harvey, has been reprinted in the Everyman's Library edition. The volume also includes some of Harvey's letters, his 'anatomical examination' of William Parr who was reputed to have died at the age of 152, and Harvey's will. Now that it is freely available again at a reasonable price, this classic should be made compulsory reading for every student of physiology. A lot more Harvey and much less coaching and cramming

CONTINUED ON PAGE 316

TB THE CHEMOTHERAPY OF TUBERCULOSIS

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would go far towards raising the standard of education of our medical students. (London: J. M. Dent & Sons Ltd., price 5s.)

The Origin of Life and the Evolution of Living Things: An Environmental Theory, by Olan R. Hyndman, M.D., propounds a theory of the origin of life on a physicochemical basis and seeks to demonstrate how the principles of this origin are continued throughout evolution. It expounds a scientific philosophy and has to make new words or give new meanings to old words to do so; it is ingenious and original, and anyone with plenty of time who enjoys playing with verbal abstracts from the concrete world will be intrigued by it. It may be an important book, but the reviewer, probably from a lack of erudition, doubts it. It is rather like the curate's first sermon—it explains everything; it is prolix; it gives the impression of a man who overwhelms one with gushes of his opinions, who talks while he thinks. Even the summary takes thirty pages, and then comes the Addendum of thirty-five! At the same time one feels that hidden in this mass of verbiage may be jewels of great price. Few practitioners will pay three guineas and have the time and patience to look for them. (New York: Philosophical Library, price $8.75.)

Psychology, the Nurse and the Patient, by Doris M. Odlum, M.R.C.S., L.R.C.P., D.P.M., 'covers the ground, from the psychological aspect, of the syllabus of the preliminary examination for State Registered Nurses. . . .' At the same time, it does more than this, as the author discusses many human problems which arise in nursing; for example, a chapter on 'the patient' deals with different personalities and their aspect to illness. This is followed by a chapter on 'the hospital and the patient', in which many problems in nursing are discussed both from the patients' points of view and those of the nursing staff. Rehabilitation, the nursing of children, and special problems in nursing are other interesting topics. (*Nursing Mirror*, Dorset House, Stamford Street, London, S.E.1, price 7s. 6d.)

The National Baby Welfare Council have recently published two pamphlets: 'Diets for Babies and Children in Health and Sickness' by Florence Dillistone, R.S.C.N., S.C.M., Dietitian, Hospital for Sick Children, Great Ormond Street (price 7½d. post free), and 'Antenatal and Postnatal Exercises' (1d.), (31 Gloucester Place, London, W.1).

Iodine Content of Foods has been compiled on the same general lines as its predecessor, 'Iodine and Plant Life', i.e. material has been collected from an annotated list of 326 scientific papers (short analyses of which are given at the end of the volume) and incorporated into nineteen tables according to food types. These tables are preceded by a short review of the literature on the subject. A classification of foods according to country of origin and a useful index are also included. (Chilean Iodine Educational Bureau, Stone House, Bishopsgate, London, E.C.2, price 21s.) In response to requests from doctors, pharmacists, and chemical manufacturers, *Iodine Pharmaceuticals*, a useful alphabetical checklist of iodine compounds and preparations used in human medicine, with a therapeutic index, has been issued price 2s. 6d.

The Foot Problem: a Plea for Preventive Action, is the title of a booklet produced by the 'Liaison Group' of the Foot Health Educational Bureau, in order to focus attention on the need for a national policy regarding preventive foot care. (121 Ebury Street, London, S.W.1.)

The Ambulatory Treatment of Ulceration of the Leg, a booklet copiously illustrated with colour photographs, describes the 'Lestreflex' Elastic Diachylon Bandage technique for treating varicose and other ulcers of the leg. The manufacturers, Messrs. Dalmas Ltd., have also sent us their new convenient 'Lestreflex' Technique Chart. (Junior Street, Leicester.)

OFFICIAL PUBLICATIONS

The Report of the Medical Research Council for the Year 1950-51, which covers the year, October 1950 to September 1951, has appeared much more promptly than its predecessor. Even so, there is still room for improvement, and it is to be hoped that the next annual report may be available within six months of the period covered. The Report shows that the Council has a staff of 1,416, made up of 434 scientific staff (153 of whom are medically qualified), 524 technical staff, 253 administrative staff, and 157 full-time and 48 part-time maintenance staff. The Council also employed, as agents for the Ministry of Health, 923 members of the Public Health Laboratory Service. For the financial year ended on March 31, 1951, the total expenditure of public funds was £1,438,277 on ordinary account and £288,443 on non-recurrent account. During the year covered by the Report the new laboratories of the Pneumoconiosis Research Unit at Cardiff were officially opened, the Group for Research on the Building Industry was dissolved, and the title of the Occupational Psychiatry Unit was changed to Unit for Research in Occupational Adaptation. The Council also assumed responsibility for providing for the research activities of the Royal Cancer Hospital, London. (H.M. Stationery Office, price 6s.)

Report of the Ministry of Health. Part II: On the State of the Public Health.—This is the

annual report of the Chief Medical Officer for the year 1950. In his introduction he reviews some of the advances in public health during the first half of the century. So far as 1950 is concerned, the outstanding features include: an infant mortality rate of 29.9, the first time a rate under 30 has been achieved in this country; a maternal mortality rate of 0.87 per thousand live births and stillbirths; 569 deaths from rheumatic fever, the lowest figure ever recorded; only 49 deaths from diphtheria; a 20 per cent. decline, compared with 1949, in the number of deaths from tuberculosis, giving the lowest figure ever recorded in this country; the clinic figures for syphilis fell from 6,812 in 1949 to 4,143 in 1950—a record low level, whilst the figures for gonorrhœa fell from 24,487 to 20,504. On the debit side is to be recorded an increase in the number of cases of food poisoning: 'Nearly half the outbreaks where the kind of food by which the infection was spread was ascertained were due to failure to maintain an adequate standard of personal and kitchen hygiene, and to faulty methods used in preparing food for large numbers'. (H.M. Stationery Office, price 6s.)

Employment Problems of Disabled Youth in Glasgow, by T. Ferguson, A. N. Macphail, and M. I. McVean, being Medical Research Council Memorandum No. 28, presents a careful and sympathetic analysis of the employment experience of two groups of young people in Glasgow: registered disabled, and children who had attended special schools for the physically handicapped and who, for various reasons, had a registration rate of only 30 per cent. A note is appended on the work of the Invalidity Insurance Court on behalf of disabled young people in Denmark, with special reference to vocational training. (H.M. Stationery Office, price 3s.)

Kwashiorkor in Africa, by J. F. Brock and M. Autret, published as No. 8 in the *World Health Organization Monograph Series*, offers a tentative definition for an ill-defined syndrome; surveys its distribution—geographically and by age; investigates the possible relation between it and adult cirrhosis and primary carcinoma of the liver; and suggests long-term measures of prevention. (H.M. Stationery Office, P.O. Box 569, price 5s.)

THE PRACTITIONER: 50 Years Ago. See page 319

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THE PRACTITIONER

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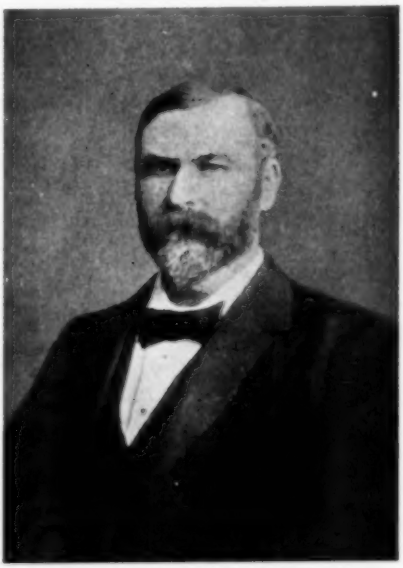
—*Jeremiah*, xxii, 7.

SEPTEMBER, 1902

A NOVEL feature at the annual dinner of the British Medical Association's meeting held at Manchester fifty years ago, was 'the allotment of separate tables to each of the sections. We have no notion [confesses the Editor] to whom the origination of this idea is due, but its "true begetter" can scarcely be congratulated on the felicity of his invention. Members of sections see quite enough of each other at their own meetings, and they have as a rule no inclination to carry their scientific discussions to the dinner table. Nevertheless all went off fairly well; the laryngologists did not fly at each other's throats, nor did the dermatologists' scalps seem to be in any danger from truculent colleagues. By a delicate irony which emphasized the absurdity of the arrangement, the only table from which there came sounds discordant with the general harmony of the banquet was that at which sat the representatives of medical ethics. But those who take upon themselves to preach the ways of professional righteousness and peace to others do not always illustrate their precepts by their example'. The editorial comments under the heading 'Rhinology and Rowdyism' are a delightful example of the lost art of polemics:—

'It is only fair to state that . . . the proceedings in the meetings of the section of ethics were so decorous as to be downright dull. The case was otherwise in certain other sections. In a piece of verse familiar to nurseries forty or fifty years ago it was related how, betwixt eyes and nose, a strange contest arose. The nose is still at war, but the contest is now with the ear and throat. The champions of those highly inflammable regions, not content with a pitched battle in the section appropriate to such debates, invaded that of children's diseases, and scared and scandalised that gentle assembly with discourse "horribly stuffed with epithets of war". No challenges, so far as we know, have been the outcome of the affair, but it would not have been surprising if some of the combatants had sought relief for the tension of the situation in a little mutual blood-letting. They would have found weapons to their hands in the tools of their handicraft. A duel between a distinguished specialist armed with a spokeshave and another doughty knight brandishing his Excalibur in the form of a tonsillotome would have supplied a really thrilling sensation for the silly season'.

To the Editor 'one of the most agreeable mementoes of the Manchester Meeting . . . will always be Professor Stirling's truly splendid



Professor William Stirling (1851-1932)

work, "Some Apostles of Physiology", which was presented to him on the occasion by the distinguished author'. William Stirling (1851-1932) was appointed Brackenbury professor of physiology in Owens College, Manchester, in 1885. An impressive figure, immaculately dressed, he was a popular speaker who illustrated his lectures with a wealth of models and historical references.

The first of the 'Original Communications', entitled 'Some Points in the Treatment of Fractures', is from the pen of W. Arbuthnot Lane, M.S., Surgeon to Guy's Hospital, and The Hospital for Sick Children: 'There is no

FIFTY YEARS AGO—*continued*

class of fractures [he writes] which I have found more difficult to treat by operation than those that come under the head of separations of epiphyses; and perhaps those particular fractures about the epiphyses which have given me the most trouble have been through the growing lines of the humerus'.

In his review of 'Diseases of the Respiratory Tract', J. J. Perkins, M.B., F.R.C.P., Assistant Physician to St. Thomas's and to the Brompton Hospital, includes a lengthy abstract of a paper by Maurice H. Richardson in *Boston Medical and Surgical Journal* (April 17, 1902) on the simulation of acute abdominal disease by pneumonia. All the cases, except one, were in children: 'The difficulty of diagnosis and the interest were increased by the pain being felt low down in the abdomen, in the right iliac fossa in fact; the thoracic symptoms under these circumstances are completely masked by the abdominal, with the result that there is an almost irresistible likeness to appendicitis. Only a knowledge of the possibility, as Richardson says, together with a routine examination of the chest in all abdominal cases, will save the physician from making a serious mistake'. Maurice Howe Richardson (1851-1912) in 1903 was appointed professor of clinical surgery at Harvard, and four years later Moseley professor of surgery. In 1911 he became surgeon-in-chief at the Massachusetts General Hospital.

All the reviews this month are of otorhinolaryngological books. 'A Treatise on Diseases of the Nose and Throat', by Ernest L. Shurly of Detroit, is described as 'lengthy and yet not exhaustive, much of it is of the "pieced together" style of workmanship, part is incorrect, and the best of the illustrations are not the original ones. . . . The mistakes in the spelling of foreign names are thick as autumn leaves in Vallombrosa. . . . On p. 593, with a fine disregard for such trivialities as precision, one author is referred to twice in the same paragraph, first as "Brunn", and six lines lower down as "Brunns". With Dr. Shurly's fatal gift for mis-spelling names, we should be inclined to regard the reference as probably to "Braun"!'. There is a nostalgic flavour about the review by Sir StClair Thomson of A. Logan Turner's 'The Accessory Sinuses of the Nose': 'In these days of hastily produced, immature books, with borrowed, smudgy process-blocks, indifferent paper, cheap printing, and flimsy binding, it is indeed a pleasure to turn to a volume which at once appeals to the bibliophile. Such a one is the work by Logan Turner on the accessory cavities of the nose. Its handsome red cloth binding is attractive, the size and weight of the volume are pleasant . . . and the illustrations are simply exquisite. That such a valuable work on such a special subject can be produced for the small price of 12*s.* is noteworthy'.

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